

Ñ – Nervous system

N02 – Analgesics

N02A – Opiates

These are all drugs deriving from opium, having analogous outcomes but also differing from it as far as power and specificity. They should have analgesic effect without being an abused drug.

N02AA – Natural Opium Alkaloids

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 46 exposures to non-specified opium alkaloids during the first 16 weeks, one newborn with congenital anomalies: ARR = 0.5 (CI 95%: 0.0-3.3).

Morphine – N02AA1

It crosses the placenta very fast.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 70 exposures during the first 16 weeks, 3 newborns with congenital anomalies: ARR = 1.0 (CI 95%: 0.3-2.9).

Case-control studies, nonspecific

- Nelson and Forfar (1971): 458 newborns with congenital anomalies, 911 healthy controls. 7 newborns exposed to morphine in the first trimester had congenital anomalies vs. 12 controls: OR = 1.2 (CI 95%: 0.5-3.0).

Feto-neonatal effects: neonatal respiratory depression when the drug was used at labor (Gilbert and Dixon 1943, Eddy et al 1957, Campbell et al 1961, Way et al 1965), reduced fetal movements (Kopecky et al 2000), withdrawal syndrome (Cobrinik et al 1959, Levy and Spino 1993, Fisher et al 1999).

N02AB – Phenylpiperidine derivatives

Pethidine (Meperidine) – N02AB02 – N02AG03 – N02AB72 – N02AB52

It crosses the placenta very fast- Patented in 1937.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 62 first trimester exposures, 3 newborns had major defects, 3 expected: RR = 1.0 (CI 95%: 0.2-2.9).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 268 exposures during the first 16 weeks, 12 newborns with congenital anomalies: ARR = 1.0 (CI 95%: 0.6-1.7).

Case-control studies, nonspecific

- Nelson and Forfar (1971): 458 newborns with congenital anomalies, 911 healthy controls. One newborn exposed to pethidine in the first trimester had minor congenital anomaly, vs. none among controls.

Feto-neonatal effects: Chronic intake or intake late in pregnancy may determine neonatal withdrawal syndrome persisting for three days (Hodgkinson and Husain 1982, Zimmer et al 1997, Sharma et al 1997), dose-depending respiratory depression (Belfrage et al 1968, Morrison et al 1973), behavioral changes and transitory EEG impairments (Borgetedt and Rosen 1968, Hodgkinson et al 1978).

Fentanyl – N01AH01 – N02AB03

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent used during the first trimester of pregnancy.

Case reports

- Regan et al (2000): 1 healthy newborn with light symptoms of withdrawal syndrome during the early 96 hours of life, exposed throughout pregnancy to transcutaneous tape with 125 µg/hour due to chronic pain.

Studies on laboratory animals

- Fujinaga et al (1987): nonteratogenic in rats Sprague-Dawley.

Feto-neonatal effects: in case of administration during labor it may cause neonatal respiratory depression (Carrie et al 1981), not observed in 137 exposures (Rayburn et al 1989); respiratory muscle rigidity (Lindemann 1988), and rhythm changes (Johnson and Colley 1980).

N02AC – Phenylpropilamine derivatives

Dextropropoxyphene – N02AC04

It is chemically similar to methadone. Patented in 1953.

We have been unable to locate references on possible human reproductive effects of this agent used during the first trimester of pregnancy.

Studies on laboratory animals

- Geber and Schramm (1975): anencephaly and cranioschisis in dose-dependent hamsters (subcutaneous 205-952 mg/kg).

Feto-neonatal effects: no changes in cardiac frequency, or respiratory depression in the newborns (Onnis et al 1983).

N02AD – Benzomorfan derivatives

Pentazocine – N02AD01

Patented in 1961.

Retrospective cohort studies without controls

- Dunn and Reynolds (1982), Chasnoff et al (1983) Chasnoff et al (1986), Little et al (1990): an overall of 57 newborns exposed throughout pregnancy as abused drug associated with tripelennamine and methylphenidate. An increased risk of birth defects in the offspring was not uncovered, while reduced intrauterine growth is attributable to the mother's abuse of alcohol, smoke etcetera.
- Von Almen and Miller (1986): 51 newborns with no congenital anomalies exposed throughout pregnancy to an illegal association of pentazocine and tripelennamine.
- Debooy et al (1933): of 39 newborns exposed throughout pregnancy to an illegal association of pentazocine and methylphenidate, 4 had congenital anomalies (IVD, polydactily and 2 twins with fetalalcoholic syndrome thus confirming multiple drug abuse).

Feto-neonatal effects: following intake of the drug just before birth a neonatal withdrawal syndrome was reported (Goets and Bain 1974, Kopelman 1975, Reeds 1975, Preis et al 1977, and Debooy et al 1993). Neonatal respiratory depression was also revealed (Freedman et al 1967, and Refstad and Lindbaek 1980).

N02AE – Oripavine derivatives

Buprenorphine – N02AE01

This is an opium alkaloyd, and its activity is morphine-like. It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent used during the first trimester of pregnancy.

Studies on laboratory animals

- Mori et al (1982): nonteratogenic in rats (0.05-5 mg/kg on day 1-17 and 17-21).
- Heel et al (1979): nonteratogenic in rats and rabbits (5 intramuscular mg/kg on day 1-17 and 17-21).

Feto-neonatal effects: following intake just before birth neonatal withdrawal syndrome was noticed (Marquet et al 1997 and Regini et al 1998), not confirmed by other studies (Celleno et al 1991, Cohen et al 1992 a, b, Lehmann et al 1992, and Roy and Basu 1992). Neonatal withdrawal syndrome (review on 309 exposures) appears to occur in 62% of the cases (Johnson et al 2003).

N02AX – More opiates

Tramadol – N02AX02

Patented in 1963.

We have been unable to locate references on possible human reproductive effects of this agent used during the first trimester of pregnancy.

Case reports

- Meyer et al (1997): 1 newborn exposed throughout pregnancy had withdrawal syndrome.

Studies on laboratory animals

- Yamamoto et al (1972): nonteratogenic in rats (60 subcutaneous and per os mg/kg).

Feto-neonatal effects: tramadol analgesic use prior to birth has revealed lower incidence on neonatal withdrawal syndrome and respiratory depression than petidine (Husslein et al 1987, Bitsch et al 1980, Suvonnakote et al 1986, Prasertsawat et al 1986, Bredow 1992, Kainz et al 1992, and Viergas et al 1993).

N02A Class Conclusions: We have not located studies suggesting risk increase of birth defects due to first-trimester exposures to this group of drugs. Their abuse may cause neonatal withdrawal syndrome and respiratory depression.

N02BA – Salicylates

Acetylsalicylic Acid – N02BA01 – A01AD05 – B01AC06 – M01BA03 – N02BA51 – N02BA71

This antiplatelet drug is a so-called NSAID and salicylate. It acts primarily by inhibiting the synthesis of prostaglandins and it is used as an anti-inflammatory, antipyretic and antirheumatic. In small doses (50-150 mg/day) it is believed to prevent pregnancy hypertension and intrauterine development retardation, but its effectiveness is not widely acknowledged. Low doses of this drug selectively inhibit tromboxane A2 production, allowing prostacycline and not causing adverse effects on mothers or their offspring (Wallenburg et al 1986, Wallemburg and Rotmans 1987, Trudiger et al 1988 and Schiff et al 1989). Pregnancy-induced hypertension, in fact, is possibly due to a modified equilibrium in the production of vascular prostacycline and tromboxane A2, the latter being increased. Aggregation and vasoconstrictive outcomes of tromboxane 2 would therefore prevail.

It is the oldest (marketed world-wide since 1899) and most used NSAID in the world.

Sistematic review

- Kozer et al (2002): a very good quality sistematic review was made through Medline and any other published study to assess the risk of birth defects following administration of aspirin in the first trimester of pregnancy. Out of 180 suitable studies 22 (15 case-control, 6 prospective or retrospective cohort studies and 1 randomized clinical trial) met all

requirements. The studies were controlled, each one with at least 6 exposures, they were in English, and period of exposure (first trimester) as well as the type of congenital anomalies were clearly recorded. It has been possible to examine specific defects, but the dosage and the reason for aspirin intake could not be scrutinized. Here are the main results:

- OR for any type of congenital anomalies in exposures during the 1st trimester, relevant to 8 studies for various defects = 1.3 (CI 95%: 0.9-1.9). The 8 studies mentioned above were divided as follows: 5 cohort studies (Turner and Collins 1975, Slone et al 1976, Newman et al 1977, Aselton et al 1985, Siffel and Czeizel 1995), 2 case-control studies (Nelson and Forfar 1971, Richards 1972) and 1 randomized study (Pattison et al 2000). When the analysis was done considering the different type of study a risk increase was highlighted in the case-control group: OR = 1.6 (CI 95%: 1.3-2.0), whereas no increase was noticed in cohort studies or in the controlled randomized study: OR = 1.0 (CI 95%: 0.9-1.1). Unfortunately there was no uniformity of results within each group, and this was probably due to the presence of recall bias in the case-control studies, where healthy newborns were chosen as controls.
- OR for CNS defects, in newborns exposed during the first trimester (1 cohort study: Slone et al 1976 and 3 case-control study: Richards 1972, Winship et al 1984, Karkinen-Jaaskelainen and Saxen 1974) = 1.4 (CI 95%: 0.9-2.2). The analysis of the case-control studies shows a risk increase: OR = 1.7 (CI 95%: 1.2-2.3), to be partially attributed to a memory bias often occurring in such studies.
- OR for DTN defects, in newborns exposed during the first trimester (3 case-control studies: Richards 1972, Lynberg et al 1994, Shaw et al 1998) = 2.2 (CI 95%: 0.9-5.2).
- OR for congenital cardiopathies in newborns exposed during the first trimester = 1.0 (CI 95%: 0.9-1.1) reported as follows: 2 cohort studies (Turner and Collins 1975, and Slone et al 1976) 4 case-control studies (Richards 1972, Zierler and Rothman 1985, Werler et al 1989, and Tikkanen and Heinonen 1992).
- OR for gastroschisis, in newborns exposed during the first trimester as in 5 case-control studies (Gierup and Lundkvist 1979, Drongowski et al 1991, Werler et al 1992, Torfs et al 1996, Martinez-Frias et al 1997) = 2.4 (CI 95%: 1.4-3.9).
- OR for gastrointestinal defects, in newborns exposed during the first trimester as in 1 cohort study (Slone et al 1976) and 1 case-control study (Richards 1972) = 1.0 (CI 95%: 0.6-1.5). They were heterogeneous studies.
- OR for oral clefts, in newborns exposed during the first trimester as in 2 case-control studies (Richards 1972 and Saxen 1975) = 2.9 (CI 95%: 2.0-4.0).
- OR for skeletal muscle defects, in newborns exposed during the first trimester as in 1 cohort study (Slone et al 1976) and 1 case-control study (Richards 1972) = 0.9 (CI 95%: 0.8-1.1).
- OR for hypospadias, in newborns exposed in the first trimester as in 2 cohort studies (Correy et al 1991 and Slone et al 1976) = 1.8 (CI 95%: 0.6-5.7).
- OR for pylorus stenosis, in newborns exposed during the first trimester as in 1 case-control study (Richards 1972) = 2.2 (CI 95%: 1.0-5.0).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 1,709 first trimester exposures, 83 newborns with major defects, 73 expected: RR = 1.1 (CI 95%: 0.9-1.4).

Case-control studies, specific

- Abe et al (2003): of 192 newborns with renal defects, 6 had been exposed in the first trimester. Of 3,029 healthy controls proportionally matched as per year and birth hospital, 29 had been exposed. AOR = 3.5 (CI 95%: 1.4 – 8.8), no difference between renal and obstructive anomalies. The exposure concerned intake of over-the-counter drugs and it is possible that the survey was influenced by a memory or interview bias.
 - Medveczky et al (2004), Hungarian CCSCA: of 1,202 newborns with DNT, 13 were exposed during the second month of gestation (critical period for DNT). Of 38,151 healthy controls, 173 were exposed with OR = 2.0 (CI 95%: 1.2-3.6) and of 22,475 controls with all the other congenital defects, 148 exposed with OR = 1.5 (CI 95%: 0.8-2.6). The result, authors suggest, should be to memory bias.

Nested case-control studies specific in the cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases with cardiovascular defects (not included those associated to chromosomal anomalies) among which 52 exposures to acetylsalicylic acid in the first trimester, and 577,730 controls out of which 5,920 exposures. OR for cardiovascular defects = 1.0 (CI 95%: 0.8-1.3).
- Kallen (2003), Swedish MBR: 1,044 cases with non-syndromic oral cleft, among which 7 exposures to acetylsalicylic acid in the first trimester, and 576,873 (in total) controls, out of which 5,920 exposures. OR = 0.7 (CI 95%: 0.3-1.4).

Feto-neonatal effects:

- Kozer et al (2003 b), meta-analysis:
 - RR for miscarriage risk, as per treatment with acetylsalicylic acid vs. placebo = 0.9 (CI 95%: 0.7-1.2). Seven studies were reported: Parazzini et al 1993, Vinikka et al 1993, CLAPS 1994, ECPPA 1996, Tulppala et al 1997, Rotchell et al 1998, and Pattison et al 2000.
 - RR for preterm birth risk, as per treatment with acetylsalicylic acid vs. placebo at every stage of pregnancy = 0.9 (CI 95%: 0.8-1.0), before week 24 of gestation = 0.9 (CI 95%: 0.8-1.0), and after week 24 of gestation = 0.9 (CI 95%: 0.4-1.0). Twenty-two studies were reported: Wallenburg et al 1986, Schiff et al 1989, Benigni et al 1989, Schrocksnadel et al 1992, Parazzini et al 1993, Hauth et al 1993, Sibai et al 1993, Caspi et al 1994, CLAPS 1994, Leslie et al 1995, ECPPA 1996, Morris et al 1996, Wang et al 1996, Gallery et al 1997, Tewari et al 1997, Hermida et al 1997, Rotchell et al 1998, Byaruhanga et al 1998, Caritis et al 1998, Golding et al 1998, Erdmann et al 1999, Pattison et al 2000)
 - RR for perinatal mortality, as per treatment with acetylsalicylic acid vs. placebo = 0.9 (CI 95%: 0.8-1.1). Twenty studies were reported: Wallenburg et al 1986, Benigni et al 1989, McParland et al 1990, Parazzini et al 1993, Sibai et al 1993, Vinikka et al 1993, Caspi et al 1994, CLAPS 1994, Leslie et al 1995, ECPPA 1996, Cowchock et al 1997, Gallery et al 1997, Hermida et al 1997, Rotchell et al 1998, Byaruhanga et al 1998, Caritis et al 1998, Golding et al 1998, McCowan et al 1999, Harrington et al 2000, Pattison et al 2000.
 - RR for gestational age retardation, as per treatment with acetylsalicylic acid vs. placebo = 1.0 (CI 95%: 0.9-1.1). Twelve studies were reported: Wallenburg et al 1986, Benigni et al 1989, Schiff et al 1989, Schrocksnadel et al 1992, Parazzini et al 1993, Sibai et al 1993, Newnham et al 1995, Morris et al 1996, Caritis et al 1998, McCowan et al 1999, Harrington et al 2000, Pattison et al 2000.
 - RR for neonatal bleeding risks, as per treatment with acetylsalicylic acid vs. placebo = 1.0 (CI 95%: 0.9-1.3). Twelve studies were reported: Schiff et al 1989, Loden et al 1992, Schrocksnadel et al 1992, Sibai et al 1993, Roy et al 1994, CLAPS 1994, Newnham et al 1995, ECPPA 1996, Rotchell et al 1998, Caritis et al 1998, Golding et al 1998, McCowan et al 1999.

The following have also been reported:

- Premature constriction of ductus arteriosus (Levin et al 1979, Perkin et al 1980, and Collins 1981). Persistent pulmonary hypertension, in one study (Alano et al 2001) assessing exposure through the analysis of NSAIDs in meconium (around half of the newborns had been exposed to aspirin), OR = 8.1 (CI 95%: 3.3-20.1).
- Congenital salicylate poisoning (Earle 1961, Levy and Garrettson 1974, and Lynd et al 1976).
- Reduced IQ for first-trimester intake (421 studied children, Streissguth et al 1987), not confirmed by further survey of the CCP data by Heinonen et al 1977. The new analysis has, in fact, revealed an increase of 2 points in the IQ of aspirin consumers' offspring, as opposed to non-consumers' offspring (study on 19,000 children, Klebanoff and Berendes 1988).

Conclusions: There are many good studies concerning first-trimester exposure to aspirin. Nonetheless the quality of each study may be biased in case-control studies, by ascertainment, or else by the difficulty of eliminating important confounding factors such as hypertermia. The overall outline provided by the systematic review and by further published studies may be summarized as follows:

- a) aspirin is not associated to a significant higher risk for congenital anomalies, and

b) an increase of specific risks (i.e. renal impairment, DTN, oral schisis or gastroschisis) should not be completely excluded.

On one hand, in fact, the risk is attributable to ascertainment bias (although this was uncovered only by case-control studies, it should be noticed that cohort studies are not sufficiently powerful to highlight modest risks for specific defects). On the other hand two items should be considered:

- a) the pharmacological effect of aspirin which includes vasoconstriction or hypoperfusion (Monada and Vane 1978, Corby 1978, and Shoenfeld et al 1980) and
- b) the lack of analogous results with paracetamol, a drug used for similar symptoms as aspirin and therefore subdue to the same ascertainment bias.

A practical approach would suggest: a) prospective prescription should consider paracetamol as a valid substitute, preferable to every other NSAID; b) in case of exposure the consultant should advice on possible, although low, risk; c) studies with no ascertainment risk should be preferred when further survey is required. Just like other prostaglandin inhibitors, intake of high doses of aspirin late in pregnancy may cause premature constriction of ductus arteriosus and possible infant pulmonary hypertension. The risk of such outcome appears very low, anyway. Aspirin is used at low doses to prevent and treat intrauterin growth retardation and gestation hypertention with no side effects. Its efficiency is, nevertheless, not proved yet (Italian Study of Aspirin in Pregnancy 1993).

Diflunisal – N02BA11

This is a derivative from acetylsalicylic acid. Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Nakatsua and Fujii (1979), Clark et al (1984): nonteratogenic in rats and rabbits at 5 and 2 times respectively the human dose. Maternal toxic doses in mothers of rabbits have uncovered an increased fetal death and vertebral anomalies.

Guacetisal – N02BA14

This agent is --- of guaiacol and acetylsalicylic acid. It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Imidazate – N02AC – N02BA16

It is available in Italy since 1983.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N02BA Class Conclusions: All our knowledge about this therapeutic class derives from studies carried out on acetylsalicylic acid during human pregnancy (see N02BA01).

N02BB Pyrazolones

Sodium metamizole (Noramidopirin – Aminopirin – Dampirone – Sulpirin – Noraminophenazone) – N02BB02 – N02BB52 – N02BB72

Patented in 1922.

Prospective cohort studies with internal controls

- Heinonen et al (1997), CPP: the drug has been evaluated along with other analgetics in 27 exposures altogether (3 of which to metamizole) during the first 16 weeks. One single newborn had congenital anomalies. ARR for the whole group = 0.8 (CI 95%: 0.1-5.6).

Case-control studies, specific

- Sharpe et al (1996): in a study carried out in Brasil 109 children had Wilms tumor. 218 controls were considered (in-patients of the same hospitals for reasons not relevant to the study). Interviews for both cases and controls were done and various possible factors of environmental risk were analyzed, including exposure to drugs in perinatal period. No association was revealed with any of the 10 pharmacologic classes taken in consideration. The analysis for specific drugs and for socio-economic standard has highlighted OR = 10.9 (CI 95%: 2.4-50.0) only for dipirone and only among the low socio-economic class. The study suggests only an hypothetical association, and very low due to the study pattern and the large number of matchings.

Feto-neonatal effects: for exposure in late pregnancy: transitory oligohydramnios (Catalan et al 1995), pulmonary hypertension (Marti Solé and Pasarisas 1996).

Propyphenazone – N02BB04 – N02BB74 – N02BB54

Patented in 1931.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Burday et al (2001): nonteratogenic in rats (210 mg/kg per os on day 8-14)

N02BB04 Class Conclusions: There is no written evidence of specific studies concerning the use of drugs belonging to this therapeutic class. As inhibitors of prostaglandin, general available information should be considered (see M01A and N02BA01).

N02BE – Anilidi

Paracetamol (Acetaminophen) – N02BE01 – N02BE51 – R01BA52 – R05DA20

This agent derives from paraminophenol and it has a light prostaglandin activity, mainly acting on CNS. Patented in 1958.

Case report

- Harley et al (1964): 1 newborn exposed in the first trimester, with congenital cataract
- Char et al (1975): 1 newborn exposed throughout pregnancy to 1.3g/day deceased for renal failure.
- Beckitt Turkel (1980): 1 newborn exposed in the 3rd-4th month of pregnancy, with hypoplasia of limbs and arthrogryposis.

Cohort studies without controls

- Riggs et al (1989), Rocky Mountain Poison and Drug Center: 60 exposures to overdose. 19 in the first trimester, 22 in the second and 33 in the third trimester of pregnancy. One single newborn with congenital defect out of those exposed in the third trimester
 - McElhatton et al (1990 and 1997), TIS in London: 300 exposures to overdose. 118 in the first, 103 in the second and 79 in the third trimester of pregnancy. 11 newborns with congenital anomalies exposed from 16th to 32nd week. 1 VIP for diaphragmatic hernia, exposed on week 18.

Retrospective cohort studies with internal controls

- Jick et al (1981), Seattle GHC: 493 first trimester exposures to paracetamol only. 3 newborns with nonspecified congenital defects (0.6%). 328 first trimester exposures to paracetamol associated with codein: 5 newborns with nonspecified congenital anomalies (1.5%). RR for any exposures = 0.8 (CI 95%: 0.4-1.7).
- Aseton et al (1985), Seattle GHC: 350 first trimester exposures to paracetamol only. 2 newborns with nonspecified congenital anomalies (0.6%). 347 first trimester exposures to

paracetamol associated with codein: 3 newborns with nonspecified congenital anomalies (0.9%). RR for any exposures = 0.5 (CI 95% 0.2-1.1).

- Rosa (1993) Michigan MSS: out of 9,146 first trimester exposures, 426 newborns had major defects, 416 expected: RR = 1.0 (CI 95%: 0.9-1.1).
- Thulstrup et al (1999), PEP Database North Jutland: 58 first trimester exposures, 7,472 controls. OR for congenital anomalies in first trimester exposures = 0.7 (CI 95%: 0.1-5.5).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 266 exposures in the early 16 weeks, 14 newborns with congenital anomalies: ARR = 1.4 (CI 95%: 0.8-2.3)

Case-controls studies, nonspecific

- Nelson and Forfar (1971): 458 newborns with congenital anomalies, 911 healthy controls. 4 newborns exposed in the first trimester to paracetamol vs 9 controls. OR = 0.9 (CI 95%: 0.2-3.2)

Case-controls studies, specific

- Winship et al (1984): 764 cases of newborns with congenital CNS anomalies. 764 healthy controls. OR for first trimester exposures to compounds containing paracetamol = 1.0 (CI 95%: 0.5-2.0).
- Zieler and Rothman (1985): 764 newborns with congenital anomalies of CNS, and 738 healthy controls. OR for first-trimester exposure to paracetamol = 1.1 (CI 90%: 0.8-1.4).
- Werler et al (1992): 76 newborns with gastroschisis, and 2,142 controls with other "major" malformations. AOR for first-trimester exposure to paracetamol = 1.7 (CI 95%: 1.0-2.9). This study has suggested a stimulating interpretation of the phenomenon as a confounding effect of hyperthermia, otherwise not confirmed by other studies.
- Torfs et al (1996): 110 newborns with gastroschisis, and 220 healthy controls. 28 newborns exposed among cases, vs. 56 among controls. AOR for first-trimester exposures to paracetamol = 0.1 (CI 95%: 0.6-1.7).
- Abe et al (2003): 192 newborns with renal system defects, 5 of which exposed in the first trimester. 3,029 healthy controls, 47 out of which exposed, proportionally matched as per year and birth hospital. AOR = 1.7 (CI 95%: 0.6-4.5). There was no difference between renal and obstructive defects.
- Cleves et al (2004): of 168 newborns, 133 had isolated defects of muscle interventricular septum of heart, in 18 of them the defects were associated with other minor defects, while in 17 cases they were in association with non-cardiac defects. 692 healthy controls. AOR for isolated muscle IVD as per exposure to paracetamol in the first trimester = 1.1 (CI 95%: 0.7-1.7). No difference between isolated and total cases, no difference between exposures in the first month prior to conception and first-trimester exposures, and no difference between exposures with or without fever.

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 newborns with cardiovascular defects (not including those associated with chromosomal anomalies), out of which 332 first-trimester exposures to paracetamol. 577,730 controls among which 36,626 exposures. OR for cardiovascular defects = 1.1 (CI 95%: 0.97-1.2).
- Kallen (2003), Swedish MBR: 1,044 cases of newborns with non-syndromic oral schisis, among which 62 exposures to paracetamol in the first trimester. 576,873 (in total) controls, among which 36,626 exposures. OR = 1.0 (CI 95%: 0.7-1.2).

Feto-neonatal effects: When toxic doses are administered during pregnancy, paracetamol may determine severe fetal hepatic adverse effects and fetal death (Rollins et al 1979, Halibach et al 1984, Wang et al 1997, Gill et al 2002). Other cases of overdose have not revealed fetal hepatotoxicity (Bayer et al 1982, Lederman et al 1983, Stokes 1984, Roberts et al 1984, Robertson et al 1986, Ludmir et al 1986, Rosevear e Hope 1989, Friedman et al 1993, McElhatton et al 1997, Sancewicz-Pach et al 1999).

For overdose on week 31st and 32nd: maternal hepatotoxicity, standstill of fetal movements, reduced cardiac frequency, neonatal hypoglycemia, temporary respiratory difficulty, and jaundice due to prematurity in a newborn appearing healthy at 6 months of age (Rosevear and Hope 1989). Premature and low-weight infants exposed to paracetamol vs. nonexposed controls and vs. exposed to aspirin have not increased cerebral hemorrhage (Rumach et al 1981). First-trimester exposures did not appear to change IQ in children tested at 4 years of age (Streissguth et al 1987). Asthma risk increased at 30-42 months of age following exposure on week 20-32, but not on <18-20 weeks (9,400 studied newborns) with OR vs. nonexposed = 2.1 (CI 95%: 1.3-3.4). No eczema increase in infants at 18-30 months of age (10,216 studied newborns) (Shaheen et al 2002).

Conclusions: None of the extensive studies found in literature concerning the use of paracetamol in the first trimester of pregnancy revealed an increased reproductive risk. No adverse effects on the newborn have been noticed following its use in other periods of pregnancy. The use of paracetamol at therapeutic dose is not causative of fetoneonatal risks and ADEC, FASS and WGZ consider it a drug of choice in pregnancy to relieve average pain and as antipyretic.

Propacetamol – N02BE05

This is injectable paracetamol. It is available in Italy since 1996.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: No specific studies have been found in literature concerning the use of this drug in human pregnancy. In case of exposure an increase in the reproductive risk is not likely, due to the lack of reported anomalies over the long period of commercialization and the chemical analogy with paracetamol, thoroughly studied.

N02BG – More analgesic and antipyretic drugs

Viminol – N02BG05

Patented in 1970.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Nefopam – N02BG06

Patented in 1969

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Case et al (1975): nonteratogenic in mice (80 mg/kg) and rabbits.

N02BG Class Conclusions: No specific studies have been found in literature concerning the use of drugs in this therapeutic class during human pregnancy. In case of exposure the following should be considered: a lack of reported anomalies over the long period of commercialization, and the absence of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases).

N02C – Antihemicrania drugs

N02CA – Ergot alkaloids

Natural ergot alkaloids increase uterine contractility and determine arterious and venous constriction.

Dihydroergotamine – N02CA01

This is a derivative of ergotamine, a vasoconstrictor with oxytocic activity. Patented in 1941.

Prospective cohort studies with internal controls

- Heinonen et al (1997), CPP: the drug has been considered along with other derivatives of ergotamine in a total of 32 exposures (3 of which to dihydroergotamine) during the first 16 weeks of pregnancy. 1 newnorn with congenital anomalies: ARR for the entire considered class = 0.7 (CI 95%: 0.1-4.8).

Feto-neonatal effects: No adverse outcomes have been noticed in 240 newborns exposed after 28th week (Goeschen et al 1984). One single preterm birth followed a treatment on week 36 (Lipper and Bohm 1984).

Ergotamine – N02CA02 – N02CA52

This is an ergot alkaloid with vasoconstrictive activity. It is used against hemicrania and as oxytocic. Patented in 1945.

Case report

- Peeden et al (1979): 1 newborn exposed per inhalation way during the early 8 weeks had imperforate anus and vagina.
- Spranger et al (1980): 1 newborn exposed in the 2nd trimester of pregnancy to ergotamine + caffeine, with hydrocephaly, sacral agenesis, digit and muscular hypoplasia, joint contracture, below average height, and SENO PILONIDALE.
- Graham et al (1983): 1 newborn exposed throughout pregnancy to high doses of ergotamine + caffeine, with jejunal atresia. The same woman had four miscarriages and one preterm birth. They had all been exposed to ergotaine.
- Hughes and Goldstein (1988): 1 newborn exposed in the first trimester to dimenhydrinate, ergotamine + caffeine + belladonna + pentobarbital, to paracetamol + codeine, and to propranolol, showing microcephaly, paraplegia, lower limb hypotonia, hip dysplasia, bilateral talipes equinovarus, lissencephaly and ventricle-megaly.
- Verloes et al (1990): 1 newborn exposed at 4 and half month of pregnancy to ergotamine + caffeine, with paraplegia and arthrogryposis.
- Graf and Shepard (1997): 1 newborn exposed to caffeine and ergotamine on day 39 of pregnancy had Moebius syndrome.

Case-control studies, nonspecific

- Czeizel (1989), Hungarian CCSCA: 9,460 newborns with congenital anomalies, 13 of which exposed, and 16,477 controls, 18 of which exposed. OR = 1.3 (CI 95%: 0.6-2.7). 4 out of 13 exposed cases showed neural tube defects, vs. none among controls.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 25 exposed in the early 16 weeks, 2 newborns with congenital anomalies. ARR = 1.8 (CI 95%: 0.5-6.7)

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: out of 59 first-trimester exposures, 9 newborns with congenital defects, 2 expected: RR = 4.5 (CI 95%: 2.1-8.5).

Feto-neonatal effects: uterine contractions and fetal tachycardy following exposure on week 38 (de Groot et al 1993), fetal death due to overdose for attempted suicide (Au et al 1985), preterm birth and neonatal death following exposure on week 34 (Hosking 1996).

N02CA Class Conclusions: Several reports on newborns exposed to ergot alkaloids (such as ergotamine and ergonovine) suggest a teratogenic effect of this rather specific drug used for hypovascular defects, since the activity of these drugs is likely to cause this type of outcomes. The risk is probably low. Prospective prescription is not recommended, but in case of exposure it is advisable to evaluate circumstances and the result of prenatal ecographies.

N02CC – Selective agonists of 5HT1-receptors

Sumatriptan – N02CC01

This selective agonist of vascular receptors of 5-hydroxytryptamine 1 is mainly found in cranial vessels and it mediate vasoconstriction. It does not affect other 5HT-receptors. It is available in Italy since 1997.

Prospective cohort studies without controls

- Wilton et al (1996): out of 35 first trimester exposures, 23 healthy newborns, 4 miscarriages, three abortions, and 5 lost during follow-up.
- Sumatriptan Pregnancy Registry (2002), Glaxo-Wellcome 1996-2002: 348 pregnancies prospectively studied, 316 of which exposed in the first trimester. 269 live births, 20 miscarriages, 11 abortions, 4 stillbirths and 12 newborns with nonspecified congenital anomalies.

Retrospective cohort studies with internal controls

- Kallen and Lygner (2001), Swedish MBR: 912 newborns exposed to antihemicranial drugs, 658 of which to sumatriptan in the first trimester. 18 newborns with congenital anomalies: OR = 0.9 (CI 95%: 0.5-1.4).

Prospective cohort studies with internal controls

- Shulhaiber et al (1998), TIS Motherisk Program: 96 exposures (95 of which in the first trimester), 96 controls with hemicrania not exposed, 96 controls exposed to nonteratogenic drugs. 1 newborn had bilateral vescicouretral reflux. The incidence of congenital anomalies did not increase in the 82 exposures, compared with the 2 control groups. RR = 1.05 vs. 90 nonexposed controls with hemicrania. RR = 1.06 vs. 91 controls exposed to nonteratogenic drugs.
- O'Quinn et al (1999), Glaxo-Wellcome: of 76 exposures to sumatriptan in the first trimester, 8 miscarriages (10.5%), 1 ectopic pregnancy (1.3%), and 67 healthy newborns. Of 92 controls exposed to sumatriptan prior to conception: 11 miscarriages (12%), 1 ectopic pregnancy, 2 abortions, 1 stillbirth, 4 newborns with minor defects, 73 healthy newborns.

Feto-neonatal effects: one survey revealed increased preterm births and low weight in exposures (Olesen et al 2000), while another one did not (Kallen and Lygner 2001).

Zolmitriptan – N02CC03

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Rizatriptan – N02CC04

It is available in Italy since 1999.

Cohort studies without controls

- Merck Pregnancy Registry for Maxalt (2002): of 29 prospective exposures, 3 miscarriages, 1 abortion (due to chromosomal anomaly), and 25 healthy newborns. Of 3 retrospective exposures: 1 anencephaly, 1 chromosomal anomaly (due to maternal age), and 1 healthy newborn.

Almotriptan – N02CC05

It is available in Italy since 2002.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Eletriptan – N02CC06

It is available in Italy since 2002.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N02CC Class Conclusions: These drugs are being marketed for relatively short time. Only sumatriptan has been sufficiently studied and we can say that the risk for congenital anomalies has not increased. As for the other drugs in this therapeutic class pharmacologic analogy should be considered.

N02CX – More antihemicrania drugs

Pizotiphen – N02CX01

This is a blocker of hystamine-H1receptors with antiserotonin activity. Patented in 1966.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Ujhazy et al (1988): nonteratogenic in mice (0.24-1.2 mg/kg per os on day 4-16).

Conclusions: There is no written evidence of specific studies concerning the use of drugs belonging to this therapeutic class in human pregnancy. In case of exposure the following should be noticed: no anomalies were reported in the period of commercialization and there is a lack of teratogenic activity on laboratory animals.

N03A – Antiepileptics

(FAE= Antiepileptics, AZL= Acetazolamide, BZD= Benzodiazepine, CBZ= Carbamazepine, CNZ= Clonazepam, DZP = Diazepam, ESM = Etosuccimide, FBM= Felbamate, GBP= Gabapentin, LTG= Lamotrigina, MPB= Metilphenobarbital, OCBZ= Oxcarbazepine, PB= Phenobarbital, PHT = Phenitoina, PRM= Primidone, SUL= Sultiame, TGB= Tiagabine, TPM= Topiramate, VGB= Vigabatrina, VPA= Valproic Acid).

Systematic review

- Gutierrez-Alvarez (2003): systematic review with good quality meta-analysis of all case-control and cohort studies (with internal controls) found through bibliography, able to supply details on the treatment and the type of observed malformations. 10 cohort and 4 case-control studies were considered (Speidel 1972, Fedrick 1973, Bjerkedal 1973, Jager Roman 1986, Martinez Frias 1990, Tanganelli and Regesta 1992, Dravet 1992, Czeizel 1992, Waters 1994, Steegers 1998, Olafsson 1998, Fonager 2000, and Holmes 2001) out of the 29 suitable found studies. (The followings were not considered: Sawhney et al 1996, Skolnik et al 1994, Diav Citrin et al 2001, Meyer 1973, Annegers et al 1974, Nakane et al 1980, Monson et al 1973, South 1972, Lowe 1973, Annegers et al 1987, Koch et al 1992, Bjerkedal e Bahna 1973, Kondo et al 1996, and Stelmasiak 2002). Cumulative OR of the 14 studies = 2.7 (CI 95%: 2.0-3.6) with an incidence of congenital defects of 9.8% among newborns exposed to FAE. (OR for several studies ranged from 0.8 and 5.1, with an average of 3.0). Despite of the large heterogeneity of the studies and some obscure gaps (nonconsidered and nonquoted studies among those not taken in consideration), this study provides the best "formal" assessment of risk associated with epilepsy treated with FAE, by the way already suggested in many reviews.

- Fried et al (2004): systematic review with good quality meta-analysis of all the studies found in the classical bibliographic sources (10 studies) providing information on cohort of newborns exposed just to maternal epilepsy, not treated with FAE during pregnancy. Ten studies, for a total of 400 newborns, revealed a cumulative OR, in comparison with newborns to mothers with no epilepsy, of 1.0 (CI 95%: 0.5-2.0). This, considering the evidence of publication bias. In these very studies OR for congenital defects associated to exposures to FAE was of 3.3 (CI 95%: 2.2-4.9), thus confirming what we had already learnt. This study clearly sets out the old question relevant to the association of the risk with FAE exposure. The risk is definitely to be attributed to FAEs, rather than epilepsy per se.
- Matalon et al (2004): systematic review having the treatment with CBZ as its main goal. Thanks to Medline 16 prospective studies have been sorted out (Hiilesma et al 1981, Kaneko et al 1988, Jones et al 1989, Van Pol et al 1991, Rosa 1991, Kaneko et al 1992, Lindhout et al 1992, Water et al 1994, Scolnik et al 1994, Ornoy e Cohen 1996, Lindhout et al 1997, Canger et al 1999, Samren et al 1999, Wide et al 2000, Diav-Citrin et al 2001, and Holmes et al 2001). Half of them were controlled studies with an overall of 1,020 exposures, the malformation incidence was as high as 6% and the cumulative weighted OR was = 2.6 (1.8-3.7). The authors also provide information on the frequency of malformations relevant to single therapies (5.5%) and polytherapies (8.6% in case of two drugs; 18.2% with more than two drugs) and it highlights that CBZ+VPA+PB therapy shows the highest risk of malformations, with an incidence of 38.5%. The most frequent malformations with CBZ alone are: cardiovascular (1.8%), urinary system (0.8%), and CNS (but only spina bifida and hydrocephaly) malformations. Oral schisis had a frequency of 0.4% for single therapy and 1.4% for polytherapy.

Literature review

- Dansky and Finnell (1991): they have published the most exhaustive literature review on epilepsy during pregnancy. 29 retrospective cohort studies published from 1938 to 1988, and 15 prospective cohort studies published from 1967 to 1990 have been examined. Most of the studies have information on the cohort of the exposures, without controls (newborns to mothers not suffering from epilepsy). The authors have summed up all of the data for each of the available studies regardless of their importance and using only some of their studies as controls, and therefore invalidating their precise analysis. As a matter of fact, this group of studies have uncovered the following trend:
 - incidence of congenital anomalies among newborns exposed to FAE around 8-10%, 2-3 times higher than among general control population;
 - incidence of congenital anomalies among mothers with epilepsy but not treated with FAE, similar to general control population (2-4%);
 - incidence of congenital cardiopathies among newborns to mothers with epilepsy treated with FAE around 2%, vs. 0.65 among nonexposed infants
 - incidence of cleft lip/palate among newborns to mothers with epilepsy treated with FAE of 1.5% vs. 0.15% among nonexposed infants.

Cohort studies concerning malformation risk

We have found a large number of cohort studies (and their reviews, as for instance: Janz 1975, Neubert e Heldge 1975, Annegers et al 1983, Kelly 1984, Holmes 1988, Mastroiacovo et al 1993, and Schardein 2000) not considered in the above mentioned reviews and substantially confirming what had been pointed out (i.e.: Heinonen et al 1977, and Rating et al 1982 comprehending a specific review concerning the effects of primidone. And also: Neri et al 1983, D'Souza et al 1991, Kaneko et al 1992, Gladstone et al 1992, Battino et al 1992, Samren et al 1997, Jick e Terris 1997, Kaneko et al 1999, and Vajda et al 2003). Some of the studies should be considered, due to their peculiarities:

- Bertollini et al (1987): 577 newborns to mothers suffering from epilepsy and treated with FAE in single therapy (PB 250, PHT 153, CBZ 70, VPA 62, and more) observed in France, Italy and Sweden. The overall incidence for malformations was of 3.5% (2.8% among PB exposures, 4.6% for PHT, 1.4 for CBZ, and 8.2 for VPA. There were no significant differences among the various drugs). The sample being so small (but homogenous) does

not bring to any conclusions but: (a) the overall incidence of malformations with monotherapeutic treatments is lower than what observed in newborns exposed to FAE (mono and polytherapies); (b) there are no important differences as far as incidence of malformations in relationship with the various single therapies; (c) the single case of spina bifida has been observed among VPA exposures and (d) there is no evidence of increased oral schisis and cardiopathy.

- King et al (1996): survey of Norwegian birth certificates over the period 1967-1992. The survey over 7,588 newborns to women suffering from epilepsy revealed that the risk for oral schisis decreased from 3.0 to 1.1 (before and after 1981), but the risk for spina bifida has increased from 1.5 to 4.4. This study shows that risks may change according to different prevailing therapies taken up at different moments.
- Canger et al (1999): prospective study done in a single center (Milan), having a good classification of defects, minor being excluded, in newborns seen at birth and at 5 days of age. 42 newborns with congenital anomalies (9.3%) were observed out of 427 FAE exposures. No congenital anomalies were uncovered among 25 women with epilepsy not exposed to FAE. The frequency of malformations among the 313 newborns exposed to single therapy was = CBZ 12/113; PB 4/83; VPA 8/44; Primidone 3/35; PHT3/31 and Clonazepam 0/6.
- Holmes et al (2001): prospective study carried out in a single center with exemplary study pattern (blind survey of studied cohorts, and very accurate definition of both major and minor malformations). 316 FAE exposures (223 in single therapy – 87 to PHT, 64 to PB, and 58 to CBZ – and 93 in polytherapy). 93 exposed to maternal positive anamnesis for epilepsy without FAE during pregnancy. 508 controls born to mothers not affected by epilepsy.

RR for any type of congenital anomalies:

- among exposed to single therapy = 2.6 (CI 95%: 0.8-8.3) with malformation incidence of 4.5%
- among exposed to polytherapy = 5.1 (CI 95%: 1.0-21.1) with malformation incidence of 8.6%
- among exposed to epilepsy alone, no FAE was not assessable with 0 cases out of 93

RR for at least one of the symptoms of FAE (major malformation, microcephaly, growth retardation, mid-facial hypoplasia, and hypoplasia of one or more fingers):

- among exposed to single therapy = 2.8 (CI 95%: 1.1-9.7) with an incidence of 20.6%
- among exposed to polytherapy = 4.2 (CI 95%: 1.1-5.1) with incidence of 28.0%
- among exposed to epilepsy alone, no FAE = 0.7 (CI 95%: 0.2-2.4) with an incidence of 6.1%.

This study shows that: (a) there is no risk for newborns to mothers suffering from epilepsy, not treated with FAE, (b) there is no substantial difference among the various drugs used in single therapy, and (c) there is a risk increase in exposed to polytherapy.

- Kaaja et al (2003), Helsinki 1980-1998: the study was done in one single maternity. 740 first trimester exposures to FAE with incidence of congenital anomalies = 3.8 (CI 95%: 2.5-5.4) and 239 not exposed to FAE but born to mothers not affected by epilepsy, with incidence of congenital defects of 0.8% (CI 95%: 0.1-3.0). The influence of FAE drugs and the absence of risk in case of epilepsy not treated during pregnancy is evident. It is worth noticing that 7 infants in the group of exposed had oral schisis (0.9%), that is a higher incidence compared to what observed in other studies, possibly due to the genetic background (Finnish people show a high incidence of oral schisis). In order to assess the influence of the various medicaments the authors have carried out a case-control study using infants not exposed to FAE as controls. AOR of general congenital anomalies in first-trimester exposures to CBZ = 2.5 (CI 95%: 1.06-6.0), to PHT = 1.7 (0.6-4.6) and to VPA = 4.1 (CI 95%: 1.6-10.5).

Case-control studies

- Czeizel et al (1992), Hungarian CCSCA: 10,698 newborns with general congenital malformations, 21,546 healthy controls. OR for FAE exposure (not including PB) based on 95 exposures = 2.9 (CI 95%: 2.1-3.8).

Case-control studies, specific

- Shaw et al (1992): 141 newborns with isolated cardiac anomalies of different types, 176 healthy controls. OR for FAE exposure = 2.5 (CI 95%: 0.2-28.0).
- Loffredo et al (1994): 450 newborns with oral schisis (354 cleft lip/palate and 96 cleft palate), 455 healthy controls. OR for FAE = 2.4 (CI 95%: 1.7-3.5).
- Arpino et al (2000), MADRE Database: out of 8,005 newborns with congenital anomalies, subjects with any registered malformations have been (in rotation) identified as cases. Subjects with other malformations, not included in the study, have been taken as controls. The analysis of exposure has been done for each FAE as per mono- and polytherapy. All OR should be interpreted with due caution, in consideration of the controls typology (exposed to other drugs and with congenital anomalies, anyway). Significant OR have been uncovered for mono-therapies:
 - with PB for cardiopathy (RR=2.2; IC 95%:1.0-4.7) and cleft lip/palate (RR=3.0; IC 95%:1.4-6.2);
 - with VPA for spina bifida (RR=7.0; IC 95%: 3.4-14.3), for cardiopathy (RR=1.7; IC 95%:1.0-2.9), for hypospadias (RR=2.5; IC 95%:1.3-5.0), for porencephaly (RR=10.9; IC 95%:1.5-48.6), for facial anomalies (RR=10.8; IC 95%:1.5-48.4), for coarctation of the aorta (RR=7.9; IC 95 %:1.1-33.2), for hypo-agenesis of limbs (RR=5.1; IC 95%:1.8-14.1);
 - with CBZ for spina bifida (RR=3.8; IC 95%:1.1-10.6).
- Medveczky et al (2004), Hungarian CCSCA: 1,202 newborns with *DTN*, 38,151 healthy controls:
 - PB 8 exposures, OR = 1.7 (IC 95%: 0.8-3.8)
 - CBZ 3 exposures, OR = 7.1 (IC 95%: 1.9-23.5)
 - PHT 1 exposure, OR = 0.9 (IC 95%: 0.1-6.6)
 - PRM 1 exposure, OR = 2.6 (IC 95%: 0.3-20.6)
 - VPA 2 exposures, OR = 11.1 (IC 95%: 2.2-57.5)

Case-control studies, specific, nested in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 19 first trimester exposures to antiepileptics out of 5,015 cases with cardiovascular anomalies (not included associated with chromosomal anomalies). 1,386 exposures out of 577,730 controls. OR for cardiovascular anomalies = 1.6 (CI 95%: 1.0-2.5).
- Kallen (2003), Swedish MBR: 5 first trimester exposures to antiepileptics out of 1,044 cases with non-syndrome cleft lip/palate. OR = 2.2 (CI 95%: 0.7-5.1).

Cohort studies to assess psychomotor developmental

- Several prospective cohort studies have surveyed the development of babies born to mothers suffering from epilepsy, treated and not treated with FAE during pregnancy, with a short follow-up (Shapiro et al 1976, Latis et al 1982, Granstrom 1982, Vert et al 1982, Jager-Roman et al 1982, Hill et al 1982, and Nomura et al 1984) or else with a more convenient follow up until school age and further (Nelson et al 1982, Hattig et al 1987, Gaily et 1988, van der Pol et al 1991, Vanoverloop et al 1992, Steinhausen et al 1994, Scolnik et al 1994, Ornoy and Cohen 1996). Every study has revealed an increased number of developmental problems associated with FAE, in particular when in polytherapy. More recent studies have made greater original contributions, or they have been able to assess the outcome of mono-therapies:
 - Koch et al (1999): prospective study on 67 school-age children and teen-agers born to mothers suffering from epilepsy, not treated with FAE during pregnancy (13), treated with FAE in mono-therapy (31) or in polytherapy (23). 49 healthy controls. IQ evaluation (Wechsler), assessment of neurobehavioral problems and EEG anomalies. The analysis has been done keeping under control the socio-economic situation of the family. EEG anomalies, neurobehavioral disorders and a low IQ revealed a decreasing frequency in treated groups exposed to polytherapy – to mono-therapy – not exposed to FAE – normal (no difference between these latest groups). Low IQ was mainly associated to primidone with dose effect.
 - Wide et al (2000): this is an intervention and evaluation study. The authors have followed a certain number of pregnancies using as much as possible FAE medicaments in single therapy and at the lowest possible dose. 100 babies underwent Griffiths' test for

psychomotor evaluation and compared to 100 controls. The test results were very similar. There was, anyway, a higher frequency of minor malformations, general and facial, in babies exposed to FAE. This study suggest that minor malformations can be prevented with more difficulties, while a regular psychomotor development, at least up to 9 months, is an easy goal.

- Holmes et al (2000): 57 children between 6 and 16 years of age born to mothers suffering from epilepsy, not treated with FAE during pregnancy (mothers were not cured, actually 53% of them started a new treatment after birth), and 57 controls, matched as per age and socio-economic status. There were no difference in their IQ, and none of the children revealed FAE dysmorphism. This study suggests that FAE and not epilepsy may be causative of intellectual impairment.
- Dessens et al (1998,1999,2000): studies on adults, carried out in Amsterdam to assess intellectual and behavioral development of in utero exposures to FAE, mainly PHT and PB, in association or alone. All studies are controlled with volunteers not exposed to FAE and matched as per sex, age and maternal age at birth. The results show slight difficulty in sense of direction, learning difficulty (worse in therapies with PHT + PB, than in mono-therapies with PB), and possible problems of sex identity.
- Adab et al (2001): retrospective study. Mothers possibly suffering from epilepsy and their school-age-children (400) were chosen and studied to assess the need for extra school help in their school activities. Data of children born to mothers exposed to FAE in mono- and polytherapy have been compared with children whose mothers had not been exposed (although suffering from epilepsy). The frequency of extra help needed for children in this latest group was of 11% (20/176). OR for FAE exposure was as follows: VPA = 3.4 (CI 95%: 1.6-7.1), CBZ = 0.3 (CI 95%: 0.1-1.2) and VPA in polytherapy = 2.5 (CI 95%: 1.0-6.1). The study highlights significant differences among various type of therapies: CBZ is less risky, whereas polytherapies and VPA are associated with greater problems.
- Gaily et al (2004): prospective study with blind control concerning intellectual development (Wechsler and variations) of children aged 5-12 years born to mothers with epilepsy, and 141 controls similar in age. Verbal IQ was: 85 (CI 95%: 80-90) in exposed to polytherapies, 82 (CI 95%: 78-87) in exposed to VPA alone, 96 (CI 95%: 93-100) in exposed to CBZ alone, and 95 (CI 95%: 92-97) in controls. The study clearly points out, once more, the differences among various therapies.

N03AA – Barbiturates and their derivatives

Phenobarbital – N03AA02

Patented in 1912.

Used as anticonvulsant.

Case report

- Bethenod and Federich (1975): 6 newborns with facies peculiare exposed during pregnancy to PB in single therapy.
- Seip (1976): two brothers with hydantoin-like fetal syndrome exposed during pregnancy to high doses of PB.
- Thakker et al (1976): 3 newborns with phalanx hypoplasia exposed to PB in mono-therapy.

Prospective cohort studies without controls

- Jones et al (1992), TIS: 76 exposures to PB early in pregnancy. 12 miscarriages, 1 abortion, 63 live births. Of 46 newborns personally examined by the authors, 7 (15%) had the typical aspect of the so-called facies syndrome (2 of them also had epispadias and inguinal hernia + DIV), 11 (24%) had unguis hypoplasia of the fifth toe. 2 out of 16 newborns revealed mental retardation.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 334 exposures to PB in the first trimester, 20 newborns had major defects, 14 expected. RR = 1.4 (CI 95%: 0.9-2.2). 8 newborns with cardiovascular defects, vs. 3 expected: RR = 2.7 (CI 95%: 1.2-5.3).

Prospective cohort studies with internal controls

- Holmes et al (2004), North American Hospital-based Registry of Pregnancies Exposed to FAE: 77 newborns to mothers prospectively enrolled prior to prenatal ecography, treated with PB in mono-therapy. Incidence of congenital anomalies = 6.5%, that is 4 times a similar analogous population-based cohort of suitable women.

Used occasionally as hypnotic/sedative drug

Perspective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 1,415 exposures to PB in the early 16 weeks, 74 newborns with congenital anomalies. RR for any type of malformations = 1.0 (CI 95%: 0.8-1.2).
- Czeizel et al (1984, 1987, 1997): around twenty women have been studied in Hungary, who attempted suicide with massive doses of PB at different moments during pregnancy. The study has not uncovered any particular risk of congenital anomalies.

Case-control studies, specific

- Rothman et al (1979): 390 newborns with cardiac defects, 1,254 healthy controls. OR for first trimester exposure to PB = 4.9 (CI 95%: 1.6-15).

Primidone – N03AA03

This drug is partially metabolized in phenobarbital. Patented in 1950.

Case-report

- Several cases of newborns showing facial dysmorphism and minor anomalies (i.e.: hypoplasia of terminal phalanx) have been reported, attributable to the so-called PHT syndrome (Goodman 1976, Lander et al 1977, Rudd and Freedom 1979, Hoyme et al 1986, Kristjansson et al 1988, Thomas and Buchanan 1981, Myhre and Williams 1981, Krauss et al 1984).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 36 first trimester exposures, 1 newborn with major defects, 2 expected. RR = 0.5 (CI 95%: 0.0-2.8).

Barbexaclone – N03AA04

This substance is obtained from the association of PB (60%) with propylhexedrine sympathomimetic (40%). It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N03AB – Hydantoin derivatives

Phenytoin – N03AB02

Patented in 1966.

Case report

Very many case reports have been published since 1968 of children born to mothers suffering from epilepsy and treated in mono-therapy or in polytherapy with other FAE medicaments. They all had a characteristic, although varied pattern of cranio-facial anomalies (short nose with wide and flat root, epicanthus, hypertelorism, low or anomalous position of ears, palpebral ptosis, strabismus, wide mouth with protruding lips, large fontanelles) sometimes associated with hands defects (hypoplasia of distal phalanx and nails, anomalies of dermatoglyphs), and, in some cases, to psychophysical retardation and/or major defects (Meadow 1968, Loughnan et al 1973, Hill et al 1973-1974, Allen et al 1980, Kousseff 1982, Allen 1984, Bostrom and Nesbit 1983, Pinto et

al 1977, Hoyt 1978, Wilson et al 1978, Apt and Gaffney 1977, Tunnesson and Lowenstein 1976, Dabee et al 1975, Taylor et al 1980, Anderson 1976, Seller et al 1979, Koussef 1981, Stankler 1980, Ringrose 1972, Pettiflor 1975, Barr et al 1974, Biale et al 1975, Yang et al 1978, Aase 1974, Pendergrass 1976, Lewin 1973, Zellweger 1974, Sherman 1976, Mallow et al 1980, Ramilo 1979, Jiminez et al 1981, Zapadlo and Kredba 1980, Bustamante 1978, Bartoshesky et al 1982, Krauss et al 1984, Verloes et al 1986, and Kotzot et al 1993). Such a pattern has been called Hanson and Smith syndrome (1975). This syndrome has been later observed also with other FAE medicaments.

In the '70ies numerous cases were reported of children exposed to PHT showing tumors (in association or non in association with dysmorphic syndrome), in particular neuroblastoma (Pendergrass and Hanson 1976, Sherman and Roizen 1976, Blattner et al 1977, Seeler et al 1979, Ramilo et al 1979, Allen et al 1980, Delgado et al 1980, Taylor et al 1980, Ehrenbard and Chaganti 1981, Jimenez et al 1981, Allen 1984, Lipson and Bale 1985, Bostrom and Nesbit 1983, Sholler et al 1987, Al Shammri et al 1992, Murray et al 1996, and Koren et al 1996). Satgé et al (1998) have made a systematic review of children tumors described in association with exposures to drugs during pregnancy. The association between neuroblastoma and PHT appears to be more than a simple hypothesis, and sufficiently proved, although the risk appears to be very low.

Cohort studies

See above. The following is worth mentioning:

- Gaily (1990) has radiologically measured phalanx bones and metacarpus of children aged around 5 and half. 76 had been exposed to the drug in the early 20 weeks (44 of them in mono-therapy), 21 exposed to other FAE drugs in the same period, 14 nonexposed children born to epileptic mothers, and 96 controls. Distal phalanx length, in particular for the 2nd and 5th toe was significantly reduced in the exposed children (11%). No other anomalies were uncovered.

Case-control studies and on cases without controls

See above. The following is worth mentioning:

- Koren et al (1989): 188 neuroblastomas were diagnosed at the Children's Hospital in Toronto between 1969 and 1988. None of them had been exposed to PHT. This study mainly suggests that neuroblastoma risk is extremely low.

N03AD – Suximide derivatives

Ethosuximide – N03AD01

Patented in 1958.

See above. Very few reports involve the exclusive use of ethosuximide. Not even one difference was detected among 13 exposures (Samren et al 1997).

N03AE – Benzodiazepine derivatives

Clonazepam – N03AE01

Patented in 1962.

Clinical reports (single therapy)

- Fisher et al (1985): 1 newborn with no congenital anomalies, exposed to CNZ throughout pregnancy, had apnea crisis, cyanosis and birth hypotonia for 10 days.

Controlled studies

- See above. No significant difference is uncovered from other FAE drugs, although clonazepam use – especially used alone – is really low (Canger et al 1999, Fisher et al 1985, Samren et al 1997 and 1999, Pardi et al 1982, Robert and Guibaud 1982, Lander and Eadie 1990, Czeizel et al 1992, Eskazan and Aslan 1992, Ornoy et al 1998, Sabers et al 1998, and Hvas et al 2000).

N03AF – Carboxinamide derivatives

Carbamazepine – N03AF01

It is available in Italy since 1960.

Review

- Rosa (1991) has worked out a specific review to assess the frequency of spina bifida after exposure to CBZ. 22 studies have been considered (Fedrick 1973, Meyer 1973, Millar and Nevin 1973, Starreveld-Zimmerman et al 1973, Barry and Danks 1974, Nakane et al 1980, Hiilesmaa et al 1981, Kuhnz et al 1983, FILAE 1984, Kelly et al 1984, Kallen et al 1986, Robert et al 1986, Bertollini et al 1987, Chitayat et al 1987, Kaneko et al 1988, Johnson et al 1989, Jones et al 1989, Lindhout 1989, Di Giambattista et al 1990, Gladstone et al 1990, Holmes et al 1990, and Rosa 1991). 984 exposures have also been assessed, 9 of which resulting in spina bifida (0.9%), 5 in single therapy (0.5%) and 4 in association (not using VPA).

Case reports

- Rosa (1995), FDA: has gathered 6 reports involving holoprosencephaly in exposures to CBZ alone (2) or in association (CBZ+PH+VPA; CBZ+PRM+PH; CBZ+GBP).
- Sutcliffe et al (1998): 4 newborns exposed during pregnancy with eye anomalies (anophthalmia; microphthalmia; coloboma).

Cohort studies

- See above. The most important fact is the absence of difference as far as global incidence of malformations in exposed to single therapies, and the specificity concerning spina bifida, with an absolute risk of 0.5-1%. The following are particularly interesting:
 - Jones et al (1989), TIS: prospective analysis of 54 newborns exposed to CBZ (48 personally examined by the author) that highlights a higher frequency of children with 3 or more minor defects in the exposures = 38 vs. 6% (p<0.001) observed among 70 nonexposed controls.
- Ornoy and Cohen (1996): 47 children between 6 months and 6 years of age exposed during pregnancy to CBZ exclusively and 47 nonexposed controls with a similar socio-economical situation. 6 exposures had minor facial dysmorphism traceable in the "CBZ syndrome". The two groups revealed identical physical growth and incidence of major birth defects. Average IQ test among exposed children was lower than among controls due to 6 newborns with dysmorphic facies, all having IQ<90. Two exposed newborns with palatoschisis had a positive family anamnesis for the same defect.

Case-control studies, specific

- See above, and:
- Kroes et al (2002), Northern Netherlands: authors have checked all data gathered in the registry for malformations of Northern Netherlands, in order to assess a connection between CBZ and ocular defects. None of the 77 cases of ocular defects (57 a-microphthalmia, 27 iridocoloboma) had been exposed to CBZ. Only 7 out of the remaining 7,271 newborns with malformations had been exposed to CBZ.

Oxcarbazepine – N03AF02

It is a carbamazepine derivative.

- See above, and see Carbamazepine, this deriving from the latter. No significant difference has been noticed with other FAE medicaments also considering that its use, mainly exclusive, is very low (Morrell 1996, Frys et al 1993, Lindhout et al 1992, Lindhout and Omtzigt 1994, Kaaja et al 2003, Samren et al 1999, Hvas et al 2000, Meischenguiser et al 2003, Isojarvi 2003, Sabers et al 1998 e 2004).

N03AG – Medicaments deriving from fat acids

Valproic acid – N03AG01

It is available in Europe since 1967.

Valpromide – N03AG02

Case reports

Since 1980 we have been able to record various case reports drawing our attention on specific adverse outcomes of VPA (at first reckoned safer than other FAE medicaments) on newborns exposed during pregnancy:

- facial dysmorphism – mid-facial hypoplasia, epicanthus, small nose, hypoplasia of nose saddle, thin upper lip, thick lower lip, and micrognathia – alone or in association with other major malformations (i.e. cleft lip or cardiopathies) (Meinardi 1977, Dalens et al 1980 and 1981, Thomas and Buchanan 1981, Clay et al 1981, Di Liberti et al 1984, Hanson et al 1984, Tein and MacGregor 1985, Winter et al 1987, Chitayat et al 1988, Palea 1991, Ishikiriyama et al 1993, Carter and Stewart 1989, Christianson et al 1994, Clayton-Smith and Donnai 1995, Moore et al 2000, and Kozma 2001);
- trigonocephaly (Ardinger et al 1988, Lajeunie et al 2001, Malm et al 2002) ;
- spina bifida (Gomez 1981, Stanley and Chambers 1982, Blaw and Woody 1983, Oakeshott and Hunt 1989);
- radial defects (Verloes et al 1990, Robert and Jouk 1991, Sharony et al 1993);
- autism was noticed more recently (Christianson et al 1994, William and Hersh 1997, Moore et al 2000, Bescoby-Chambers et al 2001, Williams et al 2001).

Case-control studies

See above: malformation risk is equal to other FAE medicaments. Valproic acid reveals a specific risk for:

- lumbosacral spina bifida (not for DNT in general: anencephaly, for instance, has been noticed very seldom and less severe forms of spina bifida are prevailing). The risk magnitude assessed in the various cohort studies (Lindhout and Schmidt 1986, Jeavons 1982, Samren et al 1997, Omtzigt et al 1992, Canger et al 1999, Moore et al 2000) and case-controls (Robert and Guibaud 1982, Mastroiacovo et al 1983, Bjerkedal et al 1982, Martinez-Frias et al 1989, Prieto and Martinez-Frias 1999, and Arpino 2000) is of 1-2% with a modest variability depending on the background defect incidence in single countries and above all on VPA administered doses.
- Hypo-agenesis of limbs, particularly pre-axial, with an absolute assessed risk of 0.42% (Rodriguez-Pinilla et al 2000);
- Hypospadias

The following is finally worth mentioning:

- Glover et al (2002): retrospective study carried out in England on 46 cases exposed to FAE medicaments, out of which 37 exposed to VPA (29 in single therapy). Myopia was noticed in 50% of the cases exposed to VPA in single therapy. Ocular defects occurred in the entire group exposed to FAE: strabismus (20%), astigmatism (24%), and anisometropia (11%).

Vigabatrine – N03AG04

It is a selective irreversible inhibitor of GABA aminotransferase, an enzyme for the degradation of GABA in the Central Nervous System. Synaptic increases in brain and spinal fluid levels are responsible for anticonvulsant activity of the drug. It is available in Italy since 2002.

Review

- Battino (2002): review of available data on new FAE medicaments. Of 107 exposed newborns, 13 had congenital anomalies.

Case report

- Cissoko et al (2002): 6 healthy newborns exposed throughout pregnancy to VGB in association with other drugs.

Prospective cohort studies without controls

- Morrell (1996): post-marketing reports of the producer. Over 80 exposures in a nonspecified period of pregnancy revealed 18% of newborns with congenital anomalies, with no similarities and all exposed to more FAE medicaments.
 - Wilton et al (1998): one newborn with hypertonia and bending shinbone, and one with plagiocephaly out of 47 exposures.

Thiagabine – N03AG06

This is a selective inhibitor of GABA re-captation in neurons and glial cells. It is available in Italy since 1997.

Review

- Battino (2002): review of available data on new FAE medicaments. One out of 9 newborn with congenital anomalies.

Cohort studies without controls

- Morrell (1996): post-marketing reports of the producer. 23 exposures in nonspecified periods of pregnancy. 1 out of 9 newborn exposed to multiple FAE medicaments had congenital anomaly.

N03AG49 – Others

Buxamine – N03AG49

Buxamine (gamma-amino-beta-hydroxybutyric acid) is a hydroxylate derivative of GABA and, along with GABA, plays an important role as inhibitory neurotransmitter. It is available in Italy since 1961.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N03AX – More Antiepileptic medicaments

Lamotrigine – N03AX09

Its chemical structure is totally different from any other FAE medicaments. It inhibits neurotransmitters with its activity on sodium canals of neuronal membrane, and it also has an inhibitory activity on dihydrofolate reductase (Sander and Patsalos 1992). It has 1-day long half-life. It is available in Italy since 1999.

Review

- Battino (2002): review of the available data on new FAE medicaments. 10 newborns with congenital anomalies out of 135 exposures.

Case report

- Cissoko et al (2002): 4 healthy newborns exposed throughout pregnancy to LTG (2 in single therapy). 1 newborn exposed throughout pregnancy to LGT and VPA had muscle aplasia of lower lip.
- Ozkinay et al (2003): 1 newborn exposed throughout pregnancy to VPA and LTG had facies dismorfica, motor retardation and cariotype 47, XXX.

Cohort studies without controls

- Morrell (1996): the manufacturer highlighted post-marketing reports concerning 53 subjects exposed during pregnancy, at non-specified moments. 2 out of the 36 newborns (exposed to FAE polytherapy) had non-specified congenital anomalies.
- Tennis et al (2002), Glaxo Smith Kline Lamotrigine Pregnancy Registry 1992-2001: case-reports from 26 countries (possible overlapping with Morrell 1996 and Quattrini et al 1996). 334 first trimester exposures to LTG alone (168) or in association with other drugs (166). Here is the incidence of congenital anomalies in exposed

- to LTG alone (3/168) = 1.8% (CI 95%: 0.5-5.5)
- to LTG + VPA (5/50) = 10% (CI 95%: 3.7-22.6)
- to LGT in association with drugs other than VPA (5/116) = 4.3% (CI 95%: 1.6-10.3).

No specific malformation pattern.

- Sabers et al (2004): 147 exposures throughout pregnancy to FAE medicaments, 51 of which to LTG. One newborn with cardiotherapy (DIV) exposed to LGT + OCBZ.

Felbamate – N03AX10

This is an anticonvulsant dicarbamate, but its activity process is still unknown. It appears to increase the convulsion threshold by preventing the very convulsion to spread out. It is available in Italy since 1995.

Review

- Battino (2002): review of the available data on new FAE medicaments, 4 healthy newborns

Cohort studies without controls

- Morrell (1996): 10 exposures at non-specified moments of pregnancy: 1 miscarriage, 2 abortions, and 7 healthy newborns.

Topiramate – N03AX11

This is a sulfamate monosaccharide. It blocks sodium canals of neuronal membrane, thus increasing GABA activity. It is available in Italy since 1999.

Review

- Battino (2002): review of the available data on new FAE medicaments. 13 newborns out of 36 had congenital anomalies.

Case reports

- Ohman et al (2002): no adverse outcomes on 5 exposed newborns that were analyzed for pharmacokinetic studies.
- Cissoko et al (2002): 1 healthy newborn exposed throughout pregnancy to TPM, had suckling problems at birth

Prospective cohort studies without controls

- Morrell (1996): the manufacturer has highlighted post-marketing results concerning 3 healthy newborns out of 8 exposures at nonspecified stages during pregnancy
- Hoyme et al (1998): 1 out of 3 newborns had been exposed to topiramate alone (700 mg/ twice a day) and showed minor multiple defects consistent with FAE syndrome
 - Wilton et al (1998): 11 healthy newborns out of 17 first trimester exposures

Gabapentine – N03AX12

It is available in Italy since 2000.

Review

- Battino (2002): review of available data on new FAE medicaments. 3 newborns with congenital anomalies out of 3 exposures

Prospective cohort studies without controls

- Morrell (1996): the manufacturer has highlighted post-marketing results concerning 10 newborns, 3 of whom with congenital anomalies, out of 15 exposures at non-specified moments during pregnancy
- Montorius (2003), Registry of Pregnancies Exposed to Gabapentin: no increase of congenital anomalies or other adverse outcomes in 44 live births exposed to topiramate.

Levetiracem – N03AX14

This is a pyrrolidine derivative, chemically not related to existent anticonvulsant activity. We do not know the process of its activity. It is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N03A Conclusions: FAE medicaments have surely been the most studied, among current marketed drugs, to assess their embio-fetal, neonatal, and long run toxicity. Despite a very wide range of surveying problems, the pattern appears now clearer, at least as far as the most commonly used FAE medicaments.

Here are the problems hampering a “simple” assessment of FAE medicaments’ toxicity during pregnancy

Problem	Reason	Consequence	Possible solution
Sample magnitude	Epilepsy during pregnancy 3-5 per thousand; overall malformations 2-4%, one by one rare	Too little cohorts of exposures, unable to give strong answers; “Long run” cohorts. Cohorts without controls.	Pre-arranged sample magnitude, fit for the study; more efficient case-controls studies, mainly when nested in cohorts with prospective ascertainment of exposure.
Basic illness	Etiological heterogeneity and seriousness within etiology itself.	It becomes a strong confounding factor; FAE exposure is not accidental; a severe type of illness probably needs poly-therapy, whereas less severe ones may suspend the treatment.	Multivariate analysis controlling as per etiological factors and seriousness indicators.
	Prognostic heterogeneity.	Heterogeneous life-style among ill people; frequent co-morbidity and need for other drugs, during pregnancy, that may interact with FAE medicaments	Multivariate analysis controlling as per socio-economic and biologic variables.
			Analysis of patients taking FAE medicaments for reasons other than epilepsy. Analysis of patients not taking FAE “only” during embryo-fetal or pregnant period.
Exposure variability	Research continuously finds more and more drugs and suggestions	Difficulty in accumulating homogeneous in time and space case histories.	Studies on homogeneous case histories.
Outcomes	Malformations, minor anomalies as indicators of changes in development, developmental and behavioral disorders.	Too often inaccurate definitions	Cohort studies with a long follow-up; case-controls studies.

Major congenital defects

A recently published meta-analysis by Gutierrez-Alvarez (2003) have provided us with firm data concerning the actual risk-rate for congenital anomalies deriving from the use of FAE medicaments. The incidence of congenital anomalies in newborns to epileptic mothers treated with FAE medicaments is of about 10%, roughly 3 times the incidence in newborns to healthy mothers similarly studied. This is a confirmation of what previously reported in several reviews. The risk is not homogeneous for every malformation, it depends on the type of exposure and, obviously, on the **ground** risk. The most common malformations among newborns exposed to FAE medicaments are therefore still congenital cardiopathies (1 out of 70, rather than 1 out of 150) and oral schisis (cleft lip 1 out of 300, rather than 1 out of 2,000 and cleft palate 1 out of 800 rather than 1 out of 2,500).

The age-old problem whether the risk is to be attributed to the very drug or to epilepsy appears to be solved thanks to a large number of studies carried out on epileptic mothers, who had not taken any drugs during pregnancy. But this is not all. Actually, such women probably did not have the same **ground** pathology as those who had to continue the therapy.

The risk associated with FAE medicaments can vary according to the therapeutic system: it increases when FAE are used in association with other drugs and at high dosage. This has been noticed several times. The association VPA + CBZ + PB appears to have the highest risk. When a drug is used alone the risk is similar. Nevertheless some differences have been noticed:

- VPA shows a higher risk for spina bifida (1-2%), and also for hypospadias, limbs pre-axial defect (rare, but specific), and other defects. Besides, it is dose-dependant.
- CBZ shows a higher risk for spina bifida (0.5%).
- PB and PHT show a higher risk for oral schisis and cardiopathy.
- PHT is more often associated with hypoplasia of nails and fingers terminal phalanx, as well as hypertelorism.

Minor congenital defects

It is pretty evident that minor defects are more frequent in newborns treated with FAE medicaments, and it sometimes appears as a specific syndrome-pattern. This seems to be more frequent with PHT, but it is not its exclusive characteristic. The frequency of PHT syndrome – or should we say FAE syndrome - (minor defects as well as psycho-motor and somatic developmental problems) is lower than what initially assessed, probably less than 5%.

Psychomotor development

Psychomotor development in children exposed to FAE medicaments may be altered. This outcome can vary depending on FAE type and illness seriousness (determining FAE suspension in pregnancy). Lack of exposure (and therefore less severe illnesses?) appears not to be associated to developmental problems. As a matter of fact, all children to epileptic mothers (treated and not treated) should be considered at risk of developmental problems and their follow-up be watching possible sensory, motor, behavioral and learning troubles, so as to offer them effective help as early as possible.

Warnings to prevent congenital defects associated with FAE medicaments

1. Professional advice to be sought and repeated prior to conception in order to evaluate possible suspension of FAE medicaments, or else identify the best therapeutic method for a successful pregnancy.
2. One-drug therapy to be preferred, as far as possible.
3. Effective minimum dose to be used, and hematic levels checked.
4. The daily dose should be well distributed (mainly VPA) all through the day.
5. Extra doses of folic acid to be administered (although its effectiveness is only proved in theory).
6. Antenatal diagnosis to be made at third-level centers.

Feto-neonatal effects: the main neonatal outcome attributed to FAE medicaments is usually withdrawal symptoms, especially following high-dose exposures late in pregnancy (Allen and Guttmacher 1990). Anecdotal reports concerning neonatal hemorrhage increase due to lack of Vitamin K have not been confirmed by a controlled study of 204 newborns to mothers treated

with FAE medicaments a short time before birth. All but one, in fact, had not been administered Vitamin K (Chouluka et al 2002). The advice for maternal prophylaxis appears therefore unwarranted. Another frequently reported outcome is loss of weight and reduced cranial circumference (Majewski and Steger 1984, Hiilesmaa et al 1981, Mastroiacovo et al 1988, Van der Pol et al 1991, Vestermark and Vestermark 1991). Neonatal hypocalcaemia (Kayemba et al 1997) should be finally noticed, as well as hypoglycemia (Thisted and Ebbesen 1993, Ebbesen et al 2000) reported in relationship with VPA.

N04 – Antiparkinson drugs

N04A – Anticholinergic drugs

N04AA – Tertiary amines

Trihexyphenidyl – N04AA01

Patented in 1949.

Case report

- Rieder et al 1975: one newborn exposed to the medicament during the first 7 months of pregnancy had multiple defects (anencephaly and cardiopathy)
- Lemoine et al (2000): one newborn exposed throughout pregnancy had hypospadias

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: the medicament has been studied along with other parasympatholytic agents in a total of 60 exposures (9 of which to trihexyphenidyl) in the early 16 weeks of pregnancy. Two newborns had congenital anomalies: ARR for the whole considered group = 0.7 (CI 95%: 0.1-3.0).

Biperiden – N04AA02

Patented in 1957.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case report

- Nako et al (2001): one healthy newborn exposed throughout pregnancy to haloperidol, biperiden, promethazine, nitrazepam and chlorpromazine had thrombocytosis and withdrawal symptoms.

Feto-neonatal effects: necrotizing enterocolitis (Meu et al 1994).

Metixene – N04AA03

Patented in 1958.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case report

- Fedrick (1973): one healthy newborn exposed during pregnancy.

Bornaprine – N04AA11

Patented in 1956.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N04AA Class Conclusions: There is no written evidence of specific studies concerning the use of drugs in this group during human pregnancy. These being anticholinergic substances, please see also what concerns atropine. Lack of teratogenic activity has been reported in laboratory animals (records provided by manufacturer for registration, not available in databases).

N04AB – Esters chemically related to antihistamines

Orphenadrine – N04AB02

Patented in 1951.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 411 first trimester exposures, 11 newborns had major defects, 16 expected. RR = 0.7 (CI 95%: 0.3-1.2).

Conclusions: We have limited specific studies concerning orphenadrine during pregnancy.

N04B – Dopaminergic Agents

N04BA – Dopa and its derivatives

Levodopa – N04BA01

This is a pro-drug of dopamine. Patented in 1963.

Carbidopa – N04BA02

This is an inhibitor of decarboxylase. Patented in 1961.

Case report

- Cook and Klawans (1985), Allain et al (1989), Balla and Sagar (1995), Bauherz (1994), Lurie et al (1996), Arai et al (1997), Nomoto et al (1997), Hagell et al (1998), Kupsch and Oertel (1998), Thulin et al (1998), Shulman et al (2000). 11 healthy newborns exposed throughout pregnancy to carbidopa and levodopa or to levodopa alone.
- Golbe (1987): 5 healthy newborns exposed to carbidopa and levodopa, and one newborn with inguinal hernia exposed to carbidopa/levodopa and amantadine.

Cohort studies without controls

- Von Graeventiz et al (1996), Roche Drug Safety Database: 6 exposures to levodopa/benserazide. 2 abortions, 1 miscarriage, 2 healthy newborns and 1 lost at follow-up.

Feto-neonatal effects: Prolactin reduction in 3rd trimester exposures (Pujol-Amat et al 1973, Kaulhausen et al 1982). No adverse outcome on mother and child for exposures after the first trimester (Pujol-Amat et al 1973, Datta et al 1976, Chajek et al 1977, Kaulhausen et al 1982).

Benserazide – N04BA02

This is an inhibitor of decarboxylase. Patented in 1962.

Case report

- Kupsch and Oertel (1998), Hagell et al (1998): 2 healthy newborns exposed throughout pregnancy to levodopa/benserazide
- Hagell et al (1998): 1 healthy newborn exposed throughout pregnancy to levodopa and benserazide, who at conception had also been exposed to selegine.

Cohort studies without controls

- Von Graeventiz et al (1996), Roche Drug Safety Database: 6 exposures to levodopa/benserazide. 2 abortions, 1 miscarriage, 2 healthy newborns and 1 lost at follow-up.

Feto-neonatal effects: there were no toxicity symptoms in the exposed at 5 months of pregnancy (Allain et al 1989).

N04BA Class Conclusions: No specific studies have been located in literature concerning the use in pregnancy of agents in this therapeutic group, due to scarce administration to fertile women. The sole possible assessment is based on the results following studies on laboratory animals that have not showed any clear teratogenic activity (records provided by manufacturer for registration, not available in databases).

N04BB – Adamantanamine derivatives

Amantadine – N04BB01

This amine is also used as antiviral agent in the treatment and prevention of A-flu. Patented in 1964.

Case report

- Nora et al (1975): 1 first-trimester exposed newborn had single ventricle and pulmonary atresia
- Cook et al (1985): 1 healthy newborn exposed throughout pregnancy to carbidopa/levodopa, and amantadine at conception.
- Golbe (1987): 1 newborn exposed throughout pregnancy to carbidopa/levodopa and amantadine had inguinal hernia
- Levy et al (1991): 2 newborns exposed prior to and during pregnancy due to maternal multiple sclerosis
- Qamar et al (1993) and Pandit et al (1994): 1 newborn exposed on week 6 and 7 of pregnancy had tetralogy of Fallot and tibial hemimelia.

Retrospective cohort studies with internal controls

- Rosa 1993, Michigan MSS: of 51 first-trimester exposures, 5 newborns had major defects, 2 expected.

Conclusions: Only one and not large study has been found in literature, and some case reports (almost all healthy newborns). In case of exposure an increased reproductive risk is not likely, in consideration of the long period of commercialization and of the substantially negative outcomes relevant to teratogenicity on laboratory animals.

N04BC – Dopamine agonists

Bromocriptine – N04BC01 – see G02CB01

Pergolide – N04BC02

It is available in Italy since 1995.

Case report

- De Mari et al (2002): one healthy newborn exposed throughout pregnancy

Cohort studies without controls

- Athens Neurosciences Manufacturer (2003): 38 pregnancies have been reported in pre-marketing period. 3 of the newborns had major defects and 2 minor defects.

Dihydroergocriptine – N04BC03

This is an ergotamine derivative. It is available in Italy since 1988.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Ropinirol – N04BC04

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent.

Pramipexol – N04BC05

It is available in Italy since 1999.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Cabergoline – N04BC06 – see G02CB03

This dopamine agonist derives from ergoline. It is available in Italy since 1994.

Lisuride – N04BC49 – G02CB02

This ergotamine derivative is a dopaminergic with oxytocic activity. It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kodama et al (1981): nonteratogenic in mice (30 mg/kg on day 6) and in rabbits (10 mg/kg per os).

Conclusions: it is not recommended during pregnancy due to its possible oxytocic activity. See also ergotamine (N02CA02).

N04BC Conclusions: Limited studies have been located in literature concerning the use during human pregnancy of agents in this therapeutic class.

N04BD – Inhibitors of B-monoaminoxidase

Selegiline – N04BD01

It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case report

- Kupsch and Oertel (1998): 1 healthy newborn followed up until 10 years of age exposed throughout pregnancy to levodopa and benserazide

Conclusions: No specific studies have been located in literature concerning the use in pregnancy of selegiline, due to rare administration to fertile women. The sole possible assessment is based on the results following studies on laboratory animals, that have not showed any clear teratogenic activity, as reported by manufacturer for registration, not available in databases.

N04BX02 – More dopaminergic agents

Entacapone – N04BX02

It is available in Italy since 1999.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: No specific studies have been located in literature concerning the use in pregnancy of entacapone, due to scarce administration to fertile women. The sole possible assessment is based on the results following studies on laboratory animals, that have not showed any clear teratogenic activity, as reported by manufacturer for registration, not available in databases.

N05 – Psycholeptic drugs

N05A – Antipsychotics

Phenothiazines

They were synthesized in Europe at the end of 19th century during a research for new coloring agents, and introduced in therapies for mental disorders in France, in 1951. From a chemical viewpoint we can divide them in: aliphatic, piperazines and piperidines.

Cohort studies without controls

- Farkas and Farkas (1971): 152 newborns exposed to low doses of phenothiazine and 162 newborns exposed to chlorpromazine + promethazine + prochlorperazine (0.61%) for gravidic hyperemesis in the first trimester. No increase of congenital anomalies was noticed (1.97).
- Milkovich and Van den Berg (1976): 543 newborns exposed in the first trimester to phenothiazine. No increase of congenital anomalies was noticed.

Prospective cohort studies with internal controls

- Rumeau-Rouquette et al (1976): 133 exposures to aliphatic phenothiazines (chlorpromazine, meto-trimeprazine, trimeprazine and oxometazine), among which 8 newborns with congenital anomalies, vs. 10,921 controls, among which 178 newborns with congenital anomalies. RR = 3.9 (CI 95%: 1.7-8.3). There were no analogies among the 8 malformations (one case with positive test for toxoplasmosis, and one newborn with genetic microcephaly). Classical example biased at publishing and due to multiple confrontations. The authors have carried out a large study on drugs and pregnancy (published by INSERM, an organization the authors worked for) evaluating all drugs. Three “statistically significant” associations were highlighted: aliphatic phenothiazines – based on 8 cases, carbamates – based on 4 cases, inhibitor of carbonic anhydrase – based on 1 case out of 5 exposures. Two papers have been published on this study, concerning the associations just mentioned and hormone problems.
- Heinonen et al (1977), CPP: 1,309 exposures in the first 16 weeks, 66 newborns with congenital defects: ARR = 1.1 (CI 95%: 0.8-1.4).

Case-control cases, nonspecific

- Greenberg et al (1977): 836 cases with congenital anomalies, among which 23 exposures, and as many healthy controls, among which 19 exposures. OR = 1.2 (CI 95%: 0.6-2.4).

Case-control cases, specific

- Rothman et al (1979): 5 exposures out of 390 newborns with cardiopathy, and 19 exposures out of as many healthy controls. OR = 4.1 (CI 95%: 1.3-13.0).
- Zierler and Rothman (1985): 5 exposures out of 298 newborns, and 13 exposures out of 738 controls. OR = 1.0 (CI 95%: 0.4-2.2).

N05AA – Phenothiazines with aliphatic lateral chain

Chlorpromazine – N05AA01

It is being used since the 1950s to treat nausea and vomit during pregnancy. It is available in Italy since 1950.

Case controls

- O’Leary and O’Leary (1964): 1 newborn exposed from 28th to 42nd day after conception (also to meclizine) missing one limb and with omphalocele.

- Vacaflor et al (1970): 1 newborn exposed in the first trimester to chlorpromazine, lithium and other drugs had multiple congenital anomalies
- Ho et al (1975): 1 newborn exposed in the first trimester to prochlorperazine and other drugs had cleft lip/palate, micrognathia, cardiopathy, hypoplasia of lower limbs, polydactyly, and hip dysplasia.
- O'Connor et al (1981), Nako et al (2001): 2 healthy newborns exposed throughout pregnancy to chlorpromazine and other drugs.

Cohort studies without controls

- Sobel (1960): No congenital anomalies were detected in the offspring of 52 pregnancies exposed from conception to the 4th month.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 6 newborns with congenital anomalies out of 142 exposures in the early 16 weeks. ARR = 0.9 (CI 95%: 0.4-2.0).

Feto-neonatal effects: newborns exposed late in pregnancy showed extrapyramidal reactions (muscular rigidity, generalized hypertonia, and tremors), transitory symptoms that can last as long as a few months (Hill et al 1966, Ayd 1968, Tamer et al 1969, Levy and Wisniewski 1974, O'Connor et al 1981). Tachypnea, hypotonia, lethargy and jaundice disappeared in 3 weeks (Hammond and Toseland 1970), respiratory impairment (Sobel 1960), paralytic ileum (Falterman and Richardson 1980), thrombocytosis and withdrawal symptoms (Nako et al 2001) were noticed.

Levomepromazine (Metotrimeprazine) – N05AA02

It is an aliphatic phenothiazine. Patented in 1958.

Case reports

- Lemoine et al (2000): 1 newborn exposed throughout pregnancy had hypospadias

Cohort studies without controls

- Rumeau-Rouquette et al (1976): 18 newborns exposed in the first trimester: 2 newborns had congenital anomalies (hydrocephalous, and cardiopathy).

Promazine N05AA03

Patented in 1950.

Case reports

- Beghi (1963): 8 healthy newborns and one stillbirth out of 9 first-trimester exposures.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 50 exposures in the early 16 weeks, two had congenital anomalies: ARR = 0.9 (CI 95%: 0.2-3.4).

N05AB – Phenothiazines with piperazine-like structure

Dixirazine – N05AB01

It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Fluphenazine – N05AB02

Patented in 1962.

Review

- De Wet (1965): 245 first-trimester exposed pregnancies. No increase of congenital anomalies in the offspring.

Case reports

- Cleary (1977) O'Connor et al (1981): 2 healthy newborns exposed throughout pregnancy
- Donaldson and Bury (1982): 1 newborn exposed monthly and throughout pregnancy to fluphenazine had cleft lip/palate, imperforate anus, hypospadias, scrotum bifidus, and facies dismorpica.
- Merlob et al (1993): 1 newborn exposed throughout pregnancy to fluphenazine and alprazolam had esophageal reflux and left hydronephrosis. A second pregnancy exposed to fluphenazine and trihexyphenidyl has resolved into a newborn with no congenital anomalies.

Retrospective cohort studies with internal controls

Rosa (1993), Michigan MSS: 13 first trimester exposures, 1 newborn with major defects, 0.6 expected. RR = 1.7 (CI 95%: 0.0-9.3).

Prospective cohort studies with internal controls

- Heinonen et al (1977) CPP: the agent has been studied along with more phenothiazines in a total of 71 exposures (9 of which to fluphenazine) occurred in the first 16 weeks, and 5 newborns had congenital anomalies. ARR for every type of malformation, for the entire surveyed group = 1.6 (CI 95%: 0.7-3.6).

Feto-neonatal effects: extrapyramidal reactions were noticed in exposures late in pregnancy (muscular rigidity, generalized hypertonia, and tremors) by Cleary 1977, O'Connor et al 1981, and Nath et al 1996).

Perphenazine – N05AB03

Patented in 1956.

Case Reports

- Wertelecki et al (1980): 1 newborn exposed to toxic doses of perphenazine and amitriptyline to commit suicide on day 8 of pregnancy caused multiple defects.

Cohort studies without controls

- Harer (1958): 56 exposures in the first trimester showed no increase of congenital anomalies.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 140 first trimester exposures, 5 newborns had major defects, 6 expected. RR = 0.8 (CI 95%: 0.3-1.9).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 63 exposures in the early 16 weeks of pregnancy, 2 newborns had congenital anomalies. ARR = 0.7 (CI 95%: 0.2-2.7).

Trifluoperazine – N05AB06

Patented in 1956.

Case Reports

- Corner (1962): a couple of twins exposed in the first six months of pregnancy, both showing hypo-agenesis of the 4 limbs.
- Canadian Department of National Health and Welfare (1962): 8 exposed newborns had hypo-agenesis of limbs.
- Hall (1963): 1 newborn exposed to trifluoperazine for 2-3 days around day 25 of gestation showed hypo-agenesis of limbs.

These reports have aroused great apprehension (thalidomide epidemic had just been identified) and were followed by further evaluations

- More cases of malformation – sacrococcyx teratoma - were reported by Bergamaschi and Berlinger (1968); Anonymous, New Zealand Committee of Adverse Drug Reaction 1968 reported anencephaly; and Vince (1969) – transposition of large vessels.

Prospective cohort studies without controls

- Manufacturer Moriarty and Nance (1963), and Schrire (1963): 480 exposures in the first half of pregnancy with incidence of congenital anomalies of 1.1%. With a control group of 8,472 the incidence was of 0.8%. The authors have therefore assessed a RR of 0.7 (CI 95%: 0.3-1.7). A malformations underestimate bias is possible in consideration of the low incidence. Later cases increased to 700 exposed pregnancies, but no significant changes were noticed (Moriarty, 1963).
- General Practitioner Research Group (1963) and Weathley (1964): 59 exposures in the first trimester showed no increase of congenital anomalies (1.7% incidence).

Retrospective cohorts studies with internal controls

- Rosa (1993), Michigan MSS: of 29 first trimester exposures, 1 newborn had major defects, 1 expected. RR = 1.0 (CI 95%: 0.0-5.6).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 42 exposures in the first 16 weeks, 3 newborns had congenital anomalies. ARR = 1.6 (CI 95%: 0.5-4.7).

Feto-neonatal effects: extrapyramidal reactions (muscular rigidity, general hypertonia, and tremors) in late-pregnancy exposures (Hill et al 1966).

N05AC – Phenothiazine with piperidine structure

Periciazine – N05AC01

Patented in 1957.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Thioridazine – N05AC02

Patented in 1966.

Case reports

- Vince (1969): 1 newborn exposed to thioridazine and trifluoperazine in the first half of pregnancy showed transposition of large vessels.

Cohort studies without controls

- Scanlon (1972): 23 healthy newborns exposed in the first trimester. The 13-years follow-up for 20 of them did not reveal any adverse outcomes.

N05AA-AB-AC Class Conclusions: We have isolated reports suggesting the hypothesis of an association between phenothiazines and hypo-agenesis of limbs, but they have not been confirmed. In case of exposure the reproductive risk-increase is not likely, in consideration of all the studies relevant to the entire group of drugs.

N05AD – Butyrophenone derivatives

LA FRASE NON HA SENSO!!!! Ecco cosa capisco:

These drugs are highly lipophilic, they easily enter brain circulation, and due to the high blood irrigation of lungs and other tissues they may be traced in urines even 6 months after the last administered dose.

Haloperidol – N05AD01

Patented in 1959.

Case reports

- Dieulangard et al (1966): 1 newborn exposed in the first trimester to haloperidol and other nonspecified drugs showed bilateral hypoplasia of limbs.
- Lemoine et al (2001): 1 newborn exposed in the first trimester had hypospadias

Case studies

- Hanson and Oakley (1975), Metropolitan Atlanta Congenital Defect Program: 86 newborns with hypo-agenesis of limbs, 38 of them had "severe defects", and none of them had been exposed to haloperidol.

Retrospective cohort studies without controls

- Godet and Marie-Cardine (1991): a study was carried out, on 199 newborns to schizophrenic mothers, using a mailing questionnaire. 29 newborns had been exposed to haloperidol in the first trimester. 3 had not severe and all different congenital anomalies.

Retrospective cohort studies with internal controls

- Van Waes and Van den Velde (1969): 98 pregnancies were exposed (90 in the first trimester and 8 in the second trimester) to low doses due to hyperemesis. There was no increase of congenital anomalies.
- Rosa (1993), Michigan MSS: of 56 first trimester exposures, 3 newborns had major defects, 2 expected. RR = 1.5 (CI 95%: 0.3-4.4).

Feto-neonatal effects: no adverse outcomes were revealed in newborns exposed after the first trimester of pregnancy or during labor (Magnier 1964, Donaldson 1982, Nurnberg 1980, Ayd 1972). One single newborn was reported to have fetal hypokinesia and oligohydramnios, following exposure to high doses due to attempted maternal suicide on week 34 (Hansen et al 1997). There were no adverse outcomes on offspring exposed throughout pregnancy relevant to neonatal weight, pregnancy term, and fetal or neonatal mortality (Van Waes and Van den Velde 1969). Sexson and Bakar noticed withdrawal symptoms (1989); thrombocytosis and withdrawal symptoms were uncovered in one newborn exposed throughout pregnancy also to biperiden, promethazine, nitrazepam and chlorpromazine (Nako et al 2001).

Conclusions: No increased risk has been found in studies on first-trimester exposures. Their use in other periods of pregnancy has not uncovered adverse outcomes on the offspring.

Pipamperone – N05AD05

Patented in 1962.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Bromperidol – N05AD06

It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Imai et al (1984): nonteratogenic in rats at doses up to 50 times therapeutic for humans

N05AF – Thioxanthen derivatives

Zuclopentixolo – N05AF05

It is available in Italy since 1991.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N05AG – Diphenyl-butyl-piperidine derivatives

Pimozide – N05AG02

Patented in 1965.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Fukuhara et al (1980) and Baldwin and Ridings (1986): nonteratogenic in rats and rabbits at doses up to 8 times therapeutic for humans.

N05AD N05AF-AG Class Conclusions: There are no specific studies in literature, consistent with the use of drugs belonging to this class in human pregnancy, except for otherwise scarce studies on haloperidol. In case of exposure the following should be considered: lack of reported increased anomalies in the period of commercialization, and of teratogenic activity on laboratory animals.

N05AH – Diazepines, Oxazepines and Thiazepines

Clozapine – N05AH02

It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case reports

- Walderman and Safferman (1993), Barnas et al (1994), Tenyi et al (1994), Di Michele et al (1996), Stoner et al (1997), Dikson et al (1998), Nguyen and Lalonde (2003): 21 healthy newborns exposed throughout pregnancy.
- Rosa (1995), FDA: adverse outcomes have been reported in exposed pregnancies. Two miscarriages, 1 abortion for nonspecified multiple defects, Turner syndrome, congenital blindness, clinodactily.

Cohort studies without controls

- Novartis Pharmacovigilance Epidemiology Service (2002) in Nguyen and Lalonde (2003): 200 cases were reported spontaneously, and the incidence of congenital anomalies was 6%. Possible bias of reports for newborns with congenital anomalies.

Feto-neonatal effects: hypocalcemia and convulsions; cerebral hemorrhage (Rosa 1995); convulsions (Stoner et al 1997); no adverse outcomes on 19 exposures (Lieberman and Safferman 1992).

Conclusions: There are limited studies on the use of clozapine in human pregnancy. In case of exposure the following should be considered: lack of reported increased anomalies in the period of commercialization, and of teratogenic activity on laboratory animals.

Olanzapine – N05AH03

It is available in Italy since 1998.

Case reports

- Malek – Ahmadi (2001), Neuman and Frasch (2001): 3 healthy newborns exposed throughout pregnancy.

Cohort studies without controls

- Lilly Worldwide Pharmacovigilance Safety Database (2001) in Carrie et al (2002): of 96 prospective exposures, 12 miscarriages (12.5%), 3 stillbirths (3.1%), 69 healthy newborns (71.9%), 2 preterm births (2.1%), and 1 newborn with nonspecified birth defect.

Feto-neonatal effects: there were no adverse outcomes on newborns exposed after the first trimester (Littrell et al 2000, Kircheiner et al 2000, and Nagy et al 2001).

Conclusions: There are limited specific studies on the use of olanzapine in pregnancy. In case of exposure the sole available information is the lack of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases).

Quetiapine – N05AH04

It is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case reports

- Tenyi et al (2002): one healthy newborn exposed to 300 mg/day during the first 20 weeks, and to 200 mg/day in the following period.

Conclusions: We have not found specific studies in literature, consistent with the use of quetiapine in human pregnancy and the only possible assessment is based on studies on laboratory animals which have not uncovered any teratogenic activity (records provided by manufacturer for registration, not available in databases).

N05AL – Benzamides

Sulpiride – N05AL01

This drug is easily eliminated: 50% of the administered dose in 8 hours and half, while 80% with 24 hours. It causes hyperprolactinemia. Patented in 1965.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Tuchmann-Duplessis (1975): no adverse outcome on rats' sexual development (30 mg/kg) from day 15 to birth.

Thiapride – N05AL03

Patented in 1973.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Suzuki et al (1985): nonteratogenic in rats (500 mg) in the organogenetic period.

Amisulpride – N05AL05

This antidopaminergic is a benzamide-substitute. It helps releasing prolactin in adenohypophysis.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Veralipride – N05AL06

It is used for menopause disorders. It is available in Italy since 1982.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Levosulpiride – N05AL49

This is a synthetic antidopaminergic drug. It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N05AL Class Conclusions: We have not found specific studies concerning the use of drugs belonging to this therapeutic class in human pregnancy. In case of exposure the following should be considered: a lack of reported increased anomalies during the period of commercialization and of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in databases).

Lithium – N05AN01

Used since 1947 in the treatment of manic-depressive syndromes.

Case reports

- Numerous congenital anomalies, particularly Ebstein anomaly or other cardiopathies were reported, concerning newborns exposed to lithium in the first trimester of pregnancy (Lewis and Suris 1970, Vacaflor 1970, Aoki and Ruedy 1971, Nora et al 1974, Weinstein 1977, Rane et al 1978, Park et al 1980, Arnon et al 1981, Allan et al 1982, Long and Willis 1984, Robert and Francannet 1990, Steffelaar and van Wesemael 1991, Filkins 1994, Eikmeier 1996, Tekin and Ellison 2000, and Lemoine et al 2001).

Cohort studies without controls

- Lithium Baby Register. This registry of babies exposed to lithium started in 1968 in Denmark and ended up gathering cases from all over the world. In theory it should have gathered all the exposed cases, but it actually recorded children with congenital anomalies showing a bias as per cardiac defects and Ebstein anomaly. The interest for this research raised particularly after Nora (1974) report. The latest report, containing data as far as march 1983, by Frankenburg and Lipinski (1983) is about a group of 275 exposed newborns. 25 had congenital anomalies, 18 of which relevant with the cardiovascular system, and 6 of which with Ebstein anomalies. Any attempt of assessment of the risk after this data is obviously totally misleading.

Retrospective cohort studies with internal controls

- Jacobson et al (1992), 4 TIS USA and Canada: 148 women were prospectively surveyed for exposure to lithium in the first trimester (average dose 927 mg/day). One abortion was reported, due to Ebstein. Incidence of congenital anomalies: 2.8%, similar to the control group (3/123: 2.4%) with one single cardiopathy (VSD). Exposed offspring showed a neonatal weight higher than the controls (3,475 g vs. 3,383 g), in spite of a similar gestation period and a prevalence of exposures to maternal smoke.
- Kallen and Tandberg (1983), Swedish MBR: after identifying all Swedish newborns to mothers having manic-depressive disorders (350) in the period 1973-1979, they have evaluated the exposure to drugs (prospectively recorded at prenatal examination. 59 had been exposed to lithium (41 to this drug alone), 7 had congenital anomalies (11.9%) (4 cardiopathies: 6.7%, no Ebstein); 228 had not been exposed to lithium (no drugs or other drugs had been administered), 9 had congenital anomalies (3.9) (2 cardiopathies: 0.9%). Women using lithium were mostly smokers.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 62 first-trimester exposures, 2 newborns had major defects, 3 expected. RR = 0.7 (CI 95%: 0.1-2.4).

Case-control studies

- E case-control studies and 2 cases only on Ebstein anomaly, one (Kallen 1988) on atresia of tricuspid, another on all malformations.

Author		Exposed cases/ total	Exposed controls/ totale	OR (IC 95%)
Kallen 1988	Ebstein	0/25	0/69	not assessable
		0/44	0/69	not assessable
Shepard and Van Allen (Warkany 1988)	Ebstein	0/16		not assessable
Sipek 1989	Ebstein	0/89		Not assessable
Zalzstein et al 1990	Ebstein	0/59	1/168	Not assessable
Edmonds and Oakley 1990	Ebstein	0/34	0/34	Not assessable
Czeizel et al 1990	All malformations	6/10.698	5/21.546	2.4 (IC 95% 0.7-9.1)
MADRE Database, 2004 (*)	Cardiopathies	2/3.041	9/12.154	0.9 (IC 95% 0.1-4.3)

* Data not published; the two exposed cardiopathies were TGV and hypoplasia of left heart; the estimate of exposure out of the control group is reasonable, such as to believe that an under-registration of exposure be lacking.

Feto-neonatal effects: nenoatal effects connected with toxicity of lithium desappear in 1-2 weeks:

- hypotonia/letargy (Wilbanks et al 1970, Silverman et al 1971, Woody et al 1971, Tunnessen and Hertz 1972, Shou et al 1973, Strothers et al 1973, Piton et al 1973, Karlsson et al 1975, Mizrahi et al 1979, Filtenborg 1982, Morrell et al 1983, Krause et al 1990, Flaherty and KrenzeloK 1997)
- cyanosis (Woody et al 1971, Tunnessen e Hertz 1972, Piton et al 1973, Rane et al 1978, Mizrahi et al 1979, Park et al 1980, Arnon et al 1981, Filtenborg 1982, Morrell et al 1983, Chapman 1989, Krause et al 1990)
- cardiomegaly (Piton et al 1973, Schou 1976, Wilson et al 1983, Morrell et al 1983, Krause et al 1990, Pinelli et al 2002)
- change in the rhythm (Tunnessen and Hertz 1972, Strothers et al 1973, Stevens et al 1974, Rane et al 1978, Park et al 1980, Arnon et al 1981, Filtenborg 1982, Wilson et al 1983, Morrell et al 1983, and Krause et al 1990)
- thyroid change (Shou et al 1973, Karlsson et al 1975, Nars and Girard 1977, Mizrahi et al 1979, Filtenborg 1982, Robert and Francannet 1990)
- diabetes insipidus(Mizrahi et al 1979, Morrell et al 1983, Ang et al 1990, Krause et al 1990, Pinelli et al 2002)
- hypoglicemy (Rane et al 1978, Mizrahi et al 1979, Morrell et al 1983, Krause et al 1990, Pinelli et al 2002)
- gastrointestinal bleeding (Stevens et al 1974)
- hepatomegaly (Morrell et al 1983, Krause et al 1990)
- polihydramnios (Krause et al 1990, Ang et al 1990).

Conclusions: Lithium may cause cardiac defects, and Ebstein anomaly in particular. The the risk assessmentinitially proposed by Nora et al (1974) for Ebstein anomaly at 2% (RR = 400, given an incidence of Ebstein anomaly of 1 out of 20,000) or at 5% (given 6 cases out of 118 surveyed in the Lithium Baby Register), and often quoted in the literature from the 70ies to the 90ies, is very probably exaggerated. None of the 208 case-controls or cases of Ebstein anomaly, in fact, had been exposed and the utmost risk is therefore less than 1%. As far as cardiopathies in general, the two cohort studies assess an absolute risk of about 3% (5 times the risk among the general population). Prenatal third-level ecography will early find out the risk probability. In conclusion, the low teratology of lithium is to be considered along with its probable efectiveness, also during pregnancy.

N05AX – More antipsychotics

Risperidone – N05AX08

It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent.

Case reports

- Mackay et al (1998): 7 healthy newborns exposed at different, not specified stages of pregnancy.
- Carrie et al (2002): 1 newborn exposed in a nonspecified period of pregnancy had agenesis of corpus callosum.
- Ratnayake and Libretto (2002): 2 healthy newborns exposed throughout pregnancy.

Studies on laboratory animals

- Van Cauteren et al (1993): nonteratogenic in rats (2.5-10 mg/kg per os).

Clothiapine – N05AX09

It is available in Italy since 1983.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kohn (1969): nonteratogenic in rabbits (6 mg/kg) and hamster (15 mg/kg).

N05AX Class Conclusions: We have not been able to find studies on the use of drugs in this class. In case of exposure a reproductive risk is not likely, in consideration of the healthy exposed offspring, the lack of anomalies during the period of commercialization, and of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases).

N05B – Anxiolytic drugs

N05BA – Benzodiazepine derivatives

Benzodiazepines (BDZ) are anticonvulsants with anxiolytic and lissive activity. They are made of a ring of benzene associated with a ring of diazepine with 7 atoms. The basic structure being modified, similar substances have been created, with qualitatively similar outcomes but having different therapeutic appliances, being quantitatively different as per pharmacodynamics and pharmacokinetics. These are liposoluble agents, having a high protein bond and classified according to their half-life in BDZ. We therefore have fast-acting drugs (< 6 hours: clonazepam, chlorazepate, midazolam and triazolam), average-acting drugs (6-24 hours: alazepam, alprazolam, chlordiazeposide, estazolam lorazepam, oxazepam and temazepam), and slow-acting drugs (>24 hours: diazepam, flurazepam and quazepam) (Goodman and Gilman 1966). They act as GABA receptors and specific receptors that exist in human embryo since the 2nd trimester. They cross the placenta and accumulate in fetal circulation 1-3 times maternal serum- levels.

Systematic review

- Dolovich et al (1998): systematic review with metanalysis of very-good quality results. Authors have used any possible source to locate 74 studies, and pick up 23 out of them responding to the required criteria (controlled studies, first-trimester exposures, malformations analyzed in a specific way). A total of 27 studies have been worked out (13 on general malformations, 11 on oral schisis alone and 3 on other malformations).

Here are the results of the systematic review with metanalysis.

Type of study	Nr of studies	Total exposures or cases	Cumulative OR (IC 95%)	Included Studies
<i>For malformations in general</i>				
Cohort study on epilepsy-free subjects	7	1,090 exposures	0.9 (0.6-1.4)	Milkovich 1974, Crombie 1975, Hartz 1975, Kullander 1976, Laegreid 1992, Pastuszak 1996, Ornoy 1997
Cohort study on epileptic subjects	2	121 exposures	1.6 (0.9-3.1)	Nakane 1980, Robert 1986
Case-control studies	4	3,897 cases	3.0 (1.3-6.8)	Greenberg 1977, Bracken 1981, Noya 1981, Laegreid 1990
<i>For orofacial schisis</i>				
Cohort, epilepsy-free	3	2,543 exposures	1.2 (0.3-4.2)	Shiono 1984, Bergman 1992, Ornoy 1997,
Cohort, epilepsy	2	121 exposures	1.0 (0.2-4.0)	Nakane 1980, Robert 1986
Case-control	6	2,847 cases	1.8 (1.1-2.8)	Safra 1975, Saxen 1975, Rosenberg 1986, Czeizel 1987-88, Laegreid 1990
<i>For cardiac malformations</i>				
Case-control	2	3,781 cases	1.6 (1.0-2.3)	Tikkanen 1992, Coreea-Villasenor 1994
<i>For CNS malformations</i>				
Case-control	1	28 cases	1.0 (0.5-2.1)	Winship 1984

The following is worth noticing:

1. One single case of orofacial-schisis occurred, out of 2,543 newborns in the three surveyed cohort studies, and, due to the "zero" levelling, the RR for each study is = 1.21!
2. Only cohort studies have been subdivided into epileptic/non-epileptic mothers. This being not valid for case-control studies. Therefore, the association emerging from case-control studies might depend on other drugs administered in the meantime to treat epilepsy.
3. There is a difference in the quality of the studies, particularly among case-control studies, where, due to the use of normal controls, are subdue to memory and interview biases. Case-control studies give a higher risk, just as an effect of such biases.
4. Case-control studies have been published after this metanalysis, not showing risk increase (see below).

We can conclude that this systematic review does not suggest any increased risk associated with BZD, if not (but very modest) associated with the use of BDZ in women with epilepsy. It also highlights that case-control studies may suggest a higher risk-increase assessment, both due to memory and interview bias and to confounding use of epileptic drugs.

More studies not used in the systematic review

Cohort studies without controls

- Czeizel and Lendvay (1989), Czeizel et al (1997), Czeizel and Monsonyi (1997): out of 559 women who attempted suicide, 8 had taken BDZ in the 3rd-4th week of gestation (5 with 90-200 mg of diazepam). There were two newborns showing congenital anomalies: 1 had bilateral cryptorchidism, the other had club foot. No "BDZ syndrome" was detected in the 58 women who had been exposed to BDZ at different stages of pregnancy.
 - Arnod and Ornoy (1992), TIS Jerusalem: 70 exposures to BDZ in pregnancy. 6 miscarriages, 9 abortions, 51 healthy newborns, 4 newborns with congenital anomalies. 2 of them, exposed to diazepam in the first trimester, had polydactily; one exposed to alprazolam had hypospadias; and the forth, also exposed to alprazolam, had Down syndrome.
- Flint et al (2000): in a study carried out in Danmark on 62 newborns exposed to maternal attempt of suicide with drugs overdose, 9 exposed within the first 90 days of gestation to BDZ did not show any congenital anomalies.

Prospective cohort studies with internal controls

- Pastuszak et al (1996), TIS Motherisk Program: 137 exposures to low doses of BDZ (43 to diazepam, 33 to lorazepam), and as many controls. 127 were exposed up to week 13, and 3 more from 14th to 26th week. One single exposed newborn showed a birth defect, vs. 3 among controls: RR = 0.4 (CI 95%: 0.0-3.4). 19 miscarriages among exposures (13.9%), vs. 10 among controls (7.3%): RR = 1.9 (CI 95%: 0.9-4.0). None of the 106 newborns had facial schisis.

Case-control studies, specific

- Aarskog (1975): 111 newborns with isolated oral schisis (99 LS and 12 PS), 362 healthy controls. 7 cases exposed in the first trimester (6.3%), vs. 4 controls (1.1%). 52 cases had family stories of oral schisis. OR = 6.0 (CI 95%: 1.6-25.0).
- Rothman et al (1979): 390 cases of newborns with cardiac defects, 15 of whom exposed; 1,254 controls, 22 of whom exposed. OR for first-trimester exposure to diazepam = 2.2 (CI 90%: 1.3-3.9).
- Zierler and Rothman (1985): 298 newborns with cardiac defects, 738 healthy newborns. OR for exposure to diazepam in the first trimester of pregnancy = 0.99 (CI 90%: 0.3-2.6).
- Bracken (1986) uses again the Bracken and Holford study (1981): 330 newborns with cardiac defects, 3,002 healthy controls. OR for first-trimester exposure = 1.6 (CI 95%: 0.9-2.9). When considering only transposition of large vessels (27 cases): OR = 3.1 (CI 95%: 0.7-13.2).
- Laegreid (1990) includes more studies published on this subject by the same group. 25 newborns with nonspecific embryopathies, non specified CNS anomalies, oral schisis, and defects of the urinary system, out of 10,646 infants born in Goteborg over the period 1985-1986. 109 controls, born after the cases. For 18 cases and 60 controls a blood sample was available, taken on the 12th week of gestation. The study was therefore based on 18 cases and 60 controls. 8 of the cases were positive to BDZ (valium in 7 of them) at an average concentration of 162 ng/ml, while 2 of the controls were (80 and 122 ng/ml). The authors affirm, then, the existence of a "BDZ syndrome", characterized by variable minor dysmorphism, CNS anomalies and defects of the urinary system, beside oral schisis associated with "high" and "not single" intake of DBZ (particularly valium). The existence of such a syndrome has been questioned by some authors (Winter 1987, Gerhardsson and Alfredsson 1987, Czeizel and Lendvay 1987, Dolovich et al 1998). As a matter of fact, none of the studies have reassessed the statement to deny it and, above all, the association with "DBZ high doses" that makes the described association "not impossible or unreasonable", has not been sufficiently analyzed. See also below.
- Correa – Villasenor et al (1994): 44 cases with Ebstein anomaly, 3,572 controls. 3 cases exposed to BDZ, vs. 35 controls: OR for anomaly of Ebstein = 5.3 (CI 95%: 1.5-18.5).
- Lagreid (1992 a-b), Viggedal et al (1993): study on psychomotor development up to 18 months, of 17 newborns exposed to therapeutic doses of BDZ, and on 29 controls not exposed to drugs. The results showed slight differences in various development tests.

Case-control studies, specific, nested in the preprospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects (not including those associated with chromosomal anomalies), out of which 15 exposures to BDZ in the first trimester, and 1,009 exposures out of 577,730 controls. OR for cardiovascular defects = 1.6 (CI 95%: 1.0-2.8).
- Kallen (2003), Swedish MBR: 1,044 cases of newborns with non-syndrome cleft lip/palate, out of which 1 exposure to BDZ in the first trimester, and 1,009 exposures out of 576,873 (in overall) controls. OR = 0.6 (CI 95%: 0.0-2.6).

Feto-neonatal effects: the use over long periods, in the last 12 weeks of pregnancy or at birth, at doses higher than 30/40 mg/day, may determine *floppy syndrome*, characterized by hyperthermia, letargy, respiratory problems and sucking difficulties (Stirrat et al 1974, Scanlon 1975, Gillberg 1977, Haram 1977, Rementeria and Bhatt 1977, Speight 1977, Woods and Malan 1978, Whitelaw et al 1981, McAuley et al 1982, Sanchis et al 1991, Perault et al 2000), apnea and hypothermia in offspring (Owen et al 1972, Cree et al 1973, Gillbert 1977, Speight 1977).

Chronic treatment may cause withdrawal symptoms – tremors, irritability, hypertonia, diarrhea and vomiting – voracious sucking, and bradycardia (Scher et al 1972, Thearle and Dunn 1973, Scanlon 1975, Athinarayanan et al 1976, Haram 1977, Mazzi 1977, Rementeria and Bhatt 1977, Backes and Cordero 1980, McAllister 1980, Van Geijn et al 1980, Kanto 1982, Barry e StClair 1987, Cerqueira et al 1988, Laegreid et al 1989), scarce fetal movement (Birger et al 1980), low weight at birth and reduced cranial circumference (Laegred et al 1992).

Diazepam – N05AB01

It may be causative of accumulation, even if administered only once a day. Patented in 1959.

Case report

- Rivas et al (1984): 1 newborn exposed 29 days after conception to 580 mg of diazepam in a single dose, had cleft lip/palate, facial asymmetry, hypertelorism and periauricular bilateral appendix.
- Lizcano-Gil et al (1995): 1 newborn exposed to 30 mg/day throughout pregnancy had onphalocele, exstrophy of the bladder, imperforate anus, bifid penis, skeletal defects, and left kidney agenesis.

Retrospective cohort studies with internal controls

- Aselton et al (1985), Seattle GHC: 1 newborn with not specified congenital anomaly (0.6%) out of 59 first trimester exposures.

Prospective cohort studies with internal controls

- Farkas (1974): 136 exposures. 84 nonexposed controls. 2.2% newborns exposed with congenital anomalies, vs. 2.38 controls.
 - Heinonen et al (1977), CPP: have considered diazepam along with other non barbituric tranquilizers and sedatives in a total of 68 exposures (10 of which to diazepam) in the early 16 weeks. 5 newborns had congenital anomalies: ARR for the entire group = 1.6 for any type of malformations (CI 95%: 0.7-3.8).

Case-control studies, specific

- Medvedzky et al (2004), Hungarian CCSCA: 25 exposures in the 2nd month of gestation (critical period for DTN), out of 1,202 newborns exposed to the drug, and 266 exposed out of 38,151 healthy controls showed an OR = 2.9 (CI 95%: 1.9-4.3), while 198 exposures out of 22,475 controls with other congenital anomalies showed OR = 2.3 (CI 95%: 1.5-2.5). Such an association has not been confirmed when their health records, used during pregnancy, have been analyzed.

Feto-neonatal effects: in case of doses over 30-40 mg or chronic treatment: *floppy syndrome* has been noticed, characterized by hypotermia, letargy, respiratory problems, and sucking difficulties (Scanlon 1975, Gillberg 1977, Haram 1977, Rementeria and Bhatt 1977, Speight 1977, Woods and Malan 1978, Perault et al 2000), and withdrawal symptoms (Flowers et al 1969, Mazzi 1977, Backers e Cordero 1980).

Chlordiazepoxide – N05BA02

It may be causative of accumulation, since it has active metabolites with a slow half-life, even when administered once a day. Patented in 1959.

Cohort studies with internal controls

- Farkas (1974): 184 exposed newborns, 84 controls. 2.17% exposed newborns with congenital anomalies, vs. 2.38% controls.
- Hartz et al (1975), CPP: 501 children exposed to chlordiazepoxide during pregnancy, 33,073 controls, surveyed in follow-up at 8 months and 4 years of age. Motor and mental tests, and IQ did not show any differences between exposed and controls.
 - Heinonen et al (1977), CPP: 11 newborns with congenital anomalies, out of 257 exposures in the first 16 weeks. ARR for every type of malformation = 0.8 (CI 95%: 0.4-1.6), for major malformations = 0.6 (CI 95%: 0.3-1.4), and for minor malformations = 1.2 (CI 95%: 0.4-2.7).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 788 first trimester exposures, 44 newborn with major defects, 34 expected: RR = 1.3 (CI 95%: 0.9-1.7). RR for cardiopathy = 1.4 (CI 95%: 0.7-2.6).

Feto-neonatal effects: for exposure close to birth: *floppy syndrome* characterized by hypothermia, letargy, respiratory problems and sucking difficulties (Bitnun 1969, Stirrat et al 1974, Athinarayanan et al 1976, Perault et al 2000).

Oxazepam – N05AB04

This is amethabolite of diazepam (see N05BA01), of prazepam and temazepam. It does not cause accumulation. Patented in 1962.

See Diazepam

Chlorazepate dipotassium – N05AB05

Patented in 1965.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case report

- Patel and Patel (1980): 1 newborn with multiple defects exposed during pregnancy.

Feto-neonatal effects: for exposure close to birth: *floppy syndrome* characterized by hypertermia, letargy, respiratory problems and sucking difficulties (Perault et al 2000).

Lorazepam – N05AB06

It does not cause accumulation. Clinically similar to diazepam. Patented in 1967.

Case report

- Di Michele et al (1966): 1 healthy newborn exposed throughout pregnancy to lorazepam and chlothiapine

Retrospective cohort studies without controls

- Bonnon et al (2003): case- control rotatory study on 13,703 newborns with malformations to evaluate possible associations with BZD. 10 cases with specific defects (including oral schisis), and controls including every other newborn with malformations not included in the cases. Case-control analysis multivaried and controlled as per age and maternal parity. The sole detected association was between lorazepam and anal atresia with AOR = 6.2 (CI 95%: 2.4-15.7). This hypothesis should be reassessed on independent material.

Feto-neonatal effects: for exposure close to birth: *floppy syndrome* characterized by hypertermia, letargy, respiratory problems and sucking difficulties (Witelaw et al 1981, McAuley et al 1982, Sanchis et al 1991).

Bromazepam – N05BA08

Patented in 1963.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Oketani et al (1973): nonteratogenic in rats at 30-40 mg/kg.

Clobazam – N05BA09

It can cause accumulation even with a single daily intake. It is used also as anticonvulsant (see N03). Patented in 1974.

Cohort studies without controls

- There are various studies in literature reporting a total of 30 healthy newborns exposed to clobazam due to maternal epilepsy (Buchan 1993, Lindhout and Omtzigt 1994, Sabers et al 1998, Samren et al 1999). More studies report newborns having congenital anomalies of different type also exposed to other FAE medicaments (Omtzigt et al 1993, Buchan 1993, Lindhout and Omtzigt 1994, McElhatton et al 1996, Samren et al 1999, Moore 2000).

Ketazolam – N05BA10

Patented in 1971.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Prazepam – N05BA11

It can cause accumulation even with a single daily intake. Patented in 1965.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kuriyama et al (1978): hydrops fetalis and tale defects in rats at maternal toxic dose (2g/kg), that is 1,700-3,300 times human therapeutic dose. Nonteratogenic at a dose (250mg/kg) 40-400 times human therapeutic dose.
- Ota et al (1979): nonteratogenic in rabbits at 8-80 times the therapeutic human dose.

Alprazolam – N05BA12

This triazole-benzodiazepine has a slow activity and does not cause accumulation, even over an extended period of time. It is similar to diazepam as far as its activity and properties. Patented in 1972.

Case reports

- Ayd (1987): 1 newborn exposed in the first 2 months with syndrome of Pierre Robin.
- BIF Italian Health Department (1988): 1 newborn exposed in the first 4 weeks had gastroschisis and dyndactily. The initial association with the drug has been excluded due to newborn caryotype, showing trisomy 13 (Patau syndrome)
- Vendittelli et al (1995): 1 newborn exposed from before conception to the 2nd month of pregnancy to alprazolam, fluoxetine, eptaminole, and vitamin B1 and B6 had lipomeningocele.

Cohort studies without controls

- St Clair and Schirmer (1992): Records provided by manufacturer. 411 voluntarily reported exposures in the first trimester: 263 healthy newborns, 13 newborns (3.2%) with congenital anomalies (hydrocephaly, interatrial defect, cardiac murmur, dysplasia of the hip, metatarsus varus, cleft palate, pyloric stenosis, ascites with bilateral hydrocele, hypospadias, trisomy 18, and lipoma), 42 miscarriages, 5 stillbirths, 88 abortions. There was no malformative pattern, or increase of congenital anomalies and of spontaneous abortions.
 - Schick-Boschetto and Zuber (1992), TIS Pregnancy Healthline Pensilvania and Pregnancy Risk Information Service New Jersey: of 161 first trimester exposures, 15 (8.15%) miscarriages, 18 abortions, 123 healthy newborns, and 5 (2.9%) newborns with congenital anomalies, including minor and less severe defects.

Feto-neonatal effects: for exposure close to birth withdrawal symptoms were noticed (Barry and StClair 1987).

Pinazepam – N05BA14

It may cause accumulation even with a single daily intake. Patented in 1973.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Scrollino et al (1975): nonteratogenic in rabbits (25 mg/kg per os) and rats (200 mg/kg per os).

Etizolam – N05BA19

Patented in 1975.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Hamada et al (1979 a,b,c): nonteratogenic in rats (100 mg/kg per os) and in rabbits (25mg/kg per os). Increased esencephaly in mice at the maximum dose of 500 mg/kg per os.

Clothiazepam – N05BA49

It is available in Italy since 1978.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N05BA Class Conclusions: We have enough studies to conclude that there is no association between first trimester use of BDZ, particularly when not administered over long periods and at normal dose, and increased risk of congenital anomalies. The hypothesis of oral schisis increase suggested by some studies has many weak points in the method (see also systematic review) and it is not supported by any recent extensive and good study.

The existence of BZD embryofetopathy (intrauterine growth retardation, peculiar dysmorphism, psychomotor retardation, CNS defects and other malformations) has been hypothesized only by Laegreid Swedish group and it can be considered only if the fetus is exposed over long periods of time and to constantly high dosages.

Following exposures late in pregnancy withdrawal symptoms have been noticed in the offspring (floppy infant syndrome). If the intake of BZD in pregnancy is essential, then the minimum dose should be administered. It is preferable to use fast-acting substances and suspend the treatment prior to birth. As far as possible behavioral alterations, observed in studies on laboratory animals, and hypothesized in some small-scale studies, they deserve more attention to aim research at such outcomes.

N05BB – Diphenylmethane derivatives

Hydroxizine – N05BB01

This antagonist of H1 receptors of histamine belongs to piperazine group. Patented in 1954.

Retrospective cohort studies with internal controls

- Rosa (1993) and Schatz & Petitti, Michigan MSS: of 828 first trimester exposures, 48 newborns with major defects, 42 expected. RR = 1.1 (CI 95%: 0.8-1.5).

Prospective cohort studies with internal controls

Erez et al (1971): randomized study in double blind with 50 mg of hydroxine to assess the efficiency of hydroxine as anti-nausea agent. One single case of malformations (not specified) was noticed out of 50 first trimester exposures.

- Kullander and Kallen (1976): out of 16 newborns exposed during pregnancy (period and dose not specified), 2 had minor birth defects.

- Heinonen et al (1977), CPP: out of 50 exposures in the first 16 weeks, one newborn had congenital anomalies. ARR = 0.44 (CI 95%: 0.1-3.1).
- Einarson et al (1993), TIS Motherisk Program: 81 exposures, 53 of which in the first trimester, and 110 controls. In the group of the exposures: 6 abortions, 3 miscarriages, 66 healthy newborns, 2 newborns with major defects (DIV, and complex cardiopathy also exposed to carbamazepine), and 4 with minor defects (hydrocele, inguinal hernia, hypothyroidism also exposed to propylthiouracil, and strabismus), vs. 5 miscarriages and 5 newborns with minor defects (dysplasia of the hip, GH deficit, short frenulum of tongue, and 2 more not specified anomalies) in the controls.

Feto-neonatal effects: withdrawal symptoms in one healthy newborn exposed throughout pregnancy (Prenner 1977), no adverse effects in another newborn exposed in the 3rd trimester (Romero et al 1983).

Conclusions: We have not been able to find studies proving a reproductive risk increase.

N05BC – Carbamates

Meprobamate – N05BC01

Patented in 1955.

Case report

- Gauthier et al (1965): 1 newborn exposed in the first trimester to meprobamate and other drugs, with partial agenesis of upper limb.
- Daube and Chou (1966): 1 newborn exposed in the first trimester to meprobamate and other drugs, with lissencephaly.
- Ringrose (1972): 1 newborn exposed in the first trimester to meprobamate and propoxyphene, with multiple defects (omphalocele, closing defect of the abdominal wall, diaphragm defect, cardiopathy, and dysplasia of the hip).
- Bogdanoff et al (1972): 1 newborn exposed in the first trimester to meprobamate and other drugs, and also LSD, with eyes defects and defects of the CNS.

Cohort studies without controls

Crombie et al (1975): of 65 newborns exposed in the first 13 weeks, 4 had unspecified congenital anomalies (5.9%).

- Czeizel and Mosonyi (1997), Hungarian CCSA: 1 newborn with bilateral cryptorchidism out of 5 first trimester exposures to high doses of meprobamate, taken to commit suicide.

Retrospective cohort studies with internal controls

- Milkovich and Van den Berg (1974), Kaiser PMCP: 158 live births exposed in the early 4 lunar months to meprobamate, 377 controls exposed to other drugs, and 199 nonexposed newborns. 10 newborns with congenital anomalies in the group of the exposed (6.3%), vs. 13 in the control group exposed to other drugs (3.4%) (RR = 1.6; CI 95%: 0.7-3.7), and vs. 10 in the group of nonexposed newborns (4.4%) (RR = 1.5; CI 95%: 0.6-3.4). The analysis of exposures within the first 42 days revealed: 8 newborns with congenital anomalies out of 66 exposures to meprobamate, vs. 7 newborns with birth defects out of 153 exposures to other drugs (RR = 2.7; CI 95%: 1.0-7.0) and 2 newborns with birth defects out of 77 nonexposed controls (RR = 4.7; CI 95%: 1.0-21.2). This survey was carried out later on, but the period of exposure and the defects are not specified.
 - Rosa (1993), Michigan MSS: 75 first trimester exposures, 3 newborns with major defects, 3 expected. RR = 1.0 (CI 95%: 0.2-2.9).

Prospective cohort studies with internal controls

- Kullander and Kallen (1976): of 263 newborns exposed during pregnancy (period of intake and dose not specified), 18 "minor" malformations (6.8%), 6 "major insignificant" (.3%), and 6 "major". 5 stillbirth.

- Heinonen et al (1977) and Hartz et al (1975), CPP: 356 exposures in the first 16 weeks, 20 newborns with congenital anomalies. ARR for every malformation = 1.2 (IC 95%: 0.3-1.4), for "major" malformations = 0.7 (CI 95%: 0.3-1.4), for "minor" malformations = 1.8 (IC 95%: 0.9-3.2). For 186 males exposed in the first 16 weeks: ARR = 3.4 (IC 95%: 1.1-7.7). This is a result obtained from the study of one single under group of exposures, without a clear biological explanation, though.

Case control studies, specific

- Saxen (1975), Finnish RCM: 599 cases of oral schisis, 37 of which exposed in the first trimester to meprobamate, diazepam and other sedatives (their number is not specified), vs. 590 healthy controls matched as per birth place, maternal residence and interviewer acquainted with the status of the interviewed (case or control). OR for oral schisis = 2.2 (CI 95%: 1.2-4.2). It is not clear how much is attributable to meprobamate or other drugs; it is not excluded that they be administered to epileptic mothers.

Conclusions: We have quite a few studies on this matter, and they appear to suggest a slight risk increase. Actually, the most common understanding is that the result might have been biased in many ways: subsequent analysis of subgroups of patients, ascertainment bias, subsequent analysis, lack of evaluation of relevant confounding factors.

N05BE – Azaspirodecandione derivatives

Buspirone – N05BE01

This anti-anxiety molecule is unrelated to benzodiazepines. Its half-life is of 2-14 hours. Patented in 1970.

Case report

- Brent and Wisner (1998): 1 healthy newborn exposed throughout pregnancy to buspirone, fluoxetine, and carbamazepine.

Prospective cohort studies without controls

- Wilton et al (1998): 13 first trimester exposures, 1 of which had a congenital anomaly (cistic fibrosis!).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 42 first trimester exposures, 1 newborn with major defects, 2 expected. RR = 0.5 (CI 95%: 0.0-2.8).

Conclusions: We have very few studies and they do not suggest any association between buspirone and risk increase for congenital anomalies. Such a risk is not likely, though, in consideration of a lack of reported anomalies over the long period of commercialization, and of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in database).

N05C – Hypnotics and sedatives

N05CD – Benzodiazepines derivatives

Please see N05BA for general information.

Flurazepam – N05CD01

This agent is similar to pro-nordiazepam. It may cause accumulation also when administered only once a day, due to its active metabolites having a long half-life. Patented in 1971.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 73 first trimester exposures, 4 had major defects, 3 expected RR = 1.3- (CI 95%: 0.3-3.7).

Nitrazepam – N05CD02

It may cause accumulation when administered over long periods of time. Patented in 1963.

Case reports

- Rane and Bjarke (1978): 1 newborn with congenital cardiopathy exposed to nitrazepam and lithium.
- Speight (1977), Nako et al (2001): 2 healthy newborns exposed throughout pregnancy.
- Uchida et al (2001): 1 newborn exposed in the early weeks of pregnancy to nitrazepam and etizolam, had cleft lip/palate.

Cohort studies without controls

- Czeizel et al (1997), Czeizel and Mosonyi (1997): of 25 exposures to overdose of nitrazepam, 6 newborns had congenital anomalies (3 of which were inguinal hernia)

Feto-neonatal effects: withdrawal symptoms (Speight 1977, Nako et al 2001).

Flunitrazepam – N05CD03

It may cause accumulation when used over long periods of time. Patented in 1963.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- McClain and Hoar (1980): nonteratogenic in rats (25 mg/kg).
- Suzuki et al (1983): dilatation of brain ventricle, visceral malformations and defect of the intraventricular septum of heart in mice and rabbits (100 mg/kg).
- Marquez-Orozco et al (2001 a, b): retinal anomalies and defect of the cerebral cortex in mice (2.5 mg/kg).

Estazolam – N05CD04

Patented in 1968.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Triazolam – N05CD05

Triazolebenzodiazepine. It does not cause accumulation, even when used over long periods of time. Patented in 1969.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Matsuo et al (1979): nonteratogenic in rats (300 mg/kg) and in rabbits (50 mg/kg).

Feto-neonatal effects: light respiratory distress in two newborns exposed throughout pregnancy (Attallah et al 1989). Respiratory distress in a newborn of 33 weeks exposed 7 hours before birth to overdose, regular development at 4 months of age (Sakai et al 1996).

Lormetazepam – N05CD06

This agent is similar to axazepam. It does not cause accumulation. Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Komada et al (1985): nonteratogenic in rats (100 mg/kg) exposed on 7th-17th day and 17th-21st day.

Temazepam – N05CD07

It is similar to oxazepam. It does not cause accumulation. It is chemically related to diazepam. Patented in 1962.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Midazolam – N05CD08

Patented in 1975

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Brotizolam – N05CD09

Thienotriazolodiazepine derivative. Patented in 1974.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Matsuo et al (1985): nonteratogenic in rats and rabbits (2.5 mg/kg).
- Hewett et al (1986): nonteratogenic in rats and rabbits (30 mg/kg).

Quazepam – N05CD10

It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects.

Studies on laboratory animals

- Black et al (1987): nonteratogenic in rats (120 mg/kg) and rabbits (40 mg/kg).

Nordazepam – N05CD49

It is available in Italy since 1973.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N05CD Class Conclusions: See Benzodiazepines N05BA

N05CF – Analogs of Benzodiazepines

Zopiclone – N05CF01

It is the progenitor of the cyclopirolones, a new class of drugs with hypnotic-sedative activity. Its half-life is of 5 hours. It is available in Italy since 1993.

Prospective cohort studies with internal controls

- Diav-Citrin et al (1999), TIS Motherisk Program: 31 newborns exposed in the first trimester to zopiclone, and 37 newborns exposed to nonteratogenic drugs. None of the exposed had congenital anomalies, vs. 1 in the control group.

Conclusions: There is no evidence of association between zopiclone and reproductive risk increase. In case of exposure such a risk is not likely, due to a lack of reported anomalies

during the period of commercialization and the absence of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in database).

Zolpidem – N05CF02

This hypnotic agent is not a benzodiazepine. It is available in Italy since 1999.

Prospective cohort studies without controls

- Wilton et al (1998): 11 healthy newborns exposed in the first trimester of pregnancy.

Conclusions: We have not been able to find specific studies on the use of this agent in human pregnancy and the sole possible evaluation is therefore based on studies on laboratory animals, which have not uncovered any teratogenic action (records provided by manufacturer, not available in database).

Zaleplon – N05CF03

This hypnotic agent is not a benzodiazepine. It is available in Italy since 2001.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are no specific studies in literature, relevant to the use of this agent in human pregnancy. The sole possible evaluation is therefore based on studies on laboratory animals, which have not revealed any teratogenic activity (records provided by manufacturer for registration, not available in database).

N05CM – More hypnotics and sedatives

Niaprazine – N05CM16

Patented in 1969.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are no specific studies in literature, relevant to the use of this agent in human pregnancy. The sole possible evaluation is therefore based on studies on laboratory animals, which have not revealed any teratogenic activity (records provided by manufacturer for registration, not available in database).

N06 – Psychoanaleptic drugs

N06A – Antidepressants

N06AA – non-selective inhibitors of monoamine re-captation

These are the most common antidepressants. They are structurally similar to phenothiazines. They are believed to act by blocking re-captation of noradrenaline and/or serotonin and/or dopamine in presynaptic neurons. They are absorbed by gastrointestinal system and have a high protein bond and easily spread over tissues. They are metabolized by the hepatic system, thus creating active metabolites. They are not active when excreted in urine. They have a long plasma half-life and easily cross the placenta, being highly liposoluble.

Retrospective cohort studies without controls

- Brunel et al (1994): of 114 first trimester exposures to antidepressants, not including anti-MAO, 24 abortions, 11 miscarriages, 1 fetal death, 74 healthy newborns – 3 of whom showing withdrawal symptoms, 4 newborns with congenital anomalies (5.1%), one of which with major defect (DIV).

Prospective cohort studies without controls

- MaElhatton et al (1996), ENTIS – 11 European TIS (2 in Italy): authors have assessed the incidence of congenital anomalies in 502 newborns to 689 women who had contacted TIS for advice at exposure. The results (see Table) do not suggest an increase in congenital anomalies, when compared with the usual incidence in the population of reference (??). There were no similar defects among the 11 observed malformations, and no case of hypogenesis of limbs was uncovered.

Groups	Exposures (n)	Exposed offspring	Congenital anomalies	Incidence (CI 95%)
Tricyclics	Amitriptyline 89, Clomipramine 88, Imipramine 27, Doxepin 8, Doxepine 7, Trimipramine 9, Dosulepine 6, Nortriptyline 4, Desipramine 2.	201	7	3.5 % (0.9%-6.0%)
Non- tricyclics	Maprotiline 77, Fluoxetine 67, Fluvoxamine 50, Mianserine 37, Amineptine 25, Viloxazine 17, Tianeptine 14, Medifoxamine 11, Paroxetine 3.	262	7	2.7 % (0.7%-4.6%)
Antidepressant polytherapies		39	0	0

Retrospective cohort studies with internal controls

- Simon et al (2002): this study was carried out to assess side effects of tricyclic antidepressants in pregnancy, with particular interest in perinatal effects. The number of first trimester exposures was not mentioned. 209 exposures to tricyclic antidepressants (49 imipramine, 36 doxepin, 33 nortriptyline, and 22 desipramine), and 209 controls. 10 exposed newborns had major birth defects, vs. 12 among controls (RR = 0.8; CI 95%: 0.4-2.0); 14 exposed newborns with minor birth defects, vs. 18 among controls (RR = 0.8; CI 95%: 0.4-1.6).

Prospective cohort studies with external controls

- Ericson et al (1999): of 980 exposures to antidepressants, 533 to a SSRI, 432 to tricyclic agents (335 clomipramine, 44 amitriptyline, 3 imipramine, 4 nortriptyline, 6 maprotiline, 2 trimipramine, 4 lofepramine, 5 moclobemide, 1 venlafaxine, and 6 mianserine), and 15 to both. 39 newborns with congenital anomalies exposed to antidepressants in general, vs. 34.4 expected (RR = 1.1; CI 95%: 0.8-1.5); 21 newborns with congenital anomalies exposed to an SSRI, vs. 18.7 expected (RR = 1.1; CI 95%: 0.7-1.7); 18 newborns with congenital anomalies exposed to tricyclic agents, vs. 15.7 expected: RR = 1.1 (CI 95%: 0.7-1.8).

Case control studies, nonspecific

- Idanpaan – Heikkila and Saxen (1973): 2,784 newborns with congenital anomalies, and as many controls. 3 cases (2 with facial schisis, and one with talipes equinus and micrognathia) exposed to tricyclic antidepressants vs. 1 control. AOR = 3.0 (CI 95%: 0.3-74.9).
 - Greenberg et al (1977): 836 newborns with different congenital anomalies and as many healthy controls. 10 exposed cases and 6 controls. OR = 1.7 (CI 95%: 0.6-5.2).

Feto-neonatal effects: the use of tricyclic antidepressants over a long period of time and/or just before birth may cause neonatal withdrawal (irritability, tachycardia, tachypnea, hypertonus and convulsions) (Webster 1973, Eggermont 1973, Ben Muze et al 1979, Ostergaard et al 1982, Shrand 1982, Cowe et al 1982, Maxwell et al 1989, Singh et al 1990, Boringa et al 1992, Bromiker et al 1994, Bloem et al 1999). No differences were noticed between the IQ of offspring exposed to tricyclic antidepressants, SSRI, and controls (Nulman et al 1997 e 2002).

Desipramine – N06AA01

This is an active metabolite of imipramine (see). As a secondary amine it has scarce parasympatholytic activity. Patented in 1959.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 31 first trimester exposures to desipramine, 1 newborn had major defects, 1 expected. RR = 1.0 (CI 95%: 0.0-5.6).

Imipramine – N06AA02

This tertiary amine is the prototype of tricyclic antidepressants. Patented in 1949.

Case report

- McBride (1972): 2 newborns with hypoplasia of lower limbs had been exposed to amitriptyline, and 1 exposed to imipramine had bilateral amelia. Mothers had reported exposure and it was impossible for ADEC (Australian Committee for pharmacological surveillance), examining the record, to acquire specific documents about the drugs prescription.

This report, published by one of the discoverers of thalidomide teratogenicity, arose a large number of evaluations. Morrow (1972), president of ADEC, following the analysis of data reported by manufacturers and by WHO, and data from New Zealand, Canada, Germany, Denmark, Sweden, Finland, England and Ireland, stated that the available data did not prove the association between limb defects and intake of imipramine during pregnancy.

- Barson (1972): 1 newborn exposed in the first trimester had cleft palate, anencephaly, suprarenal hypoplasia and diaphragmatic hernia.
- Kuenssemberg and Knox (1972): 2 newborns with diaphragmatic hernia, 1 with abdominal muscles defects, 1 with polycystic kidney, all exposed in the first trimester.
- Ware and De Vane (1990): 2 healthy newborns exposed throughout pregnancy.

Cohort studies without controls

- Jacobson (1972), manufacturer: 14 cases of congenital anomalies, all dissimilar from each other, in exposures to imipramine over a period of 14 years of commercialization. The period of exposure is not specified.

Retrospective cohort studies without controls

- Grabowsky et al (1966): 20 healthy newborns exposed in the first trimester.
- Scanlon (1969): 20 healthy newborns exposed in the first trimester.
- Sim (1972): 81 exposures to imipramine in unspecified periods of pregnancy, but for not less than 2 months. None of the exposed showed congenital anomalies.
- Crombie et al (1972): 19 healthy newborns exposed in the first trimester.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 75 first trimester exposures, 6 newborns had major defects, 3 expected: RR = 2.0 (CI 95%: 0.7-4.4); RR for cardiovascular defects (3 detected, out of 8 expected) = 3.8 (CI 95%: 0.8-11.0).

Prospective cohort studies with internal controls

- Kullander and Kallen (1976): 13 healthy newborns exposed throughout pregnancy.

- Heinonen et al (1977), CPP: of 161 first trimester exposures to imipramine, 6 had congenital anomalies. ARR = 0.8 (CI 95%: 0.4-1.8).

Conclusions: The large number of studies, most of which never published, known when teratogenicity doubts were arisen, excludes a risk increase in malformations, particularly limb defects.

Clomipramine – N06AA04

This analog of imipramine inhibits re-captation of noradrenaline and serotonin released in the synaptic space. Patented in 1955.

Amitriptyline – N06AA09

It inhibits the re-captation of noradrenaline and serotonin in pre-synaptic process. Patented in 1958.

Case report

- McBride (1972): see imipramine

Case control studies, nonspecific

- Bracken and Holford (1981): 1,370 cases with congenital anomalies, 3 of which exposed to amitriptyline in the first trimester (but we do not know which ones), vs. 2,968 controls, none of which exposed. The association statistically significant (OR not assessable, $p = 0.03$), based on 3 cases only (possible bias: multiple confrontation, subgroups analysis).

Retrospective cohort studies without controls

- Crombie et al (1972): 19 healthy newborns exposed in the first trimester.
- Kuenssberg and Knox (1972): 31 healthy newborns exposed in the first trimester.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 467 exposures to amitriptyline, 25 major malformations, 20 expected; RR = 1.3 (CI 95%: 0.8-2.8).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 86 exposures in the early 16 weeks, 3 newborns with congenital anomalies. ARR = 0.8 (CI 95%: 0.3-2.3).

Nortriptyline – N06AA10 – N06CA49

This active metabolite of amitriptyline inhibits re-captation of noradrenaline and serotonin in adrenergic neurons. This being a secondary amine, it has minor anticholinergic effects. Patented in 1961.

Case Report

- Bourke GM (1974): 1 newborn with limb anomalies exposed to nortriptyline and other tricyclic antidepressants but not exposed in the critical period for limb development.
- Hendrick (1997): 3 healthy newborns exposed in the first trimester.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 61 exposures to nortriptyline in the first trimester, 2 newborns with major defects, 0.5 expected. RR = 4.0 (CI 95%: 0.5-14.4).

Feto-neonatal effects: neonatal urinary retention (Shearer et al 1972).

Dosulepine – N06AA16

This metabolite is active in imipramine and it inhibits re-captation of noradrenaline and serotonin. Patented in 1961.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Nakamura et al (1983): nonteratogenic in rats (40 mg/kg per os) and rabbits (80 mg/kg per os).

Maprotiline – N06AA21

It inhibits re-captation of noradrenaline and serotonin in presynaptic process. Patented in 1964.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 13 exposures to Maprotiline in the first trimester, 2 newborns had major defects.

N06AA Class Conclusions: In consideration of the large number of studies, particularly dedicated to some active principles in this therapeutic class, and due to pharmacological analogy among them, there is no evidence of association between tricyclic antidepressants and reproductive risk increase. It would be useful, in the future, to reconsider the hypothesis of association between amitriptyline and congenital cardiopathy, highlighted by a Swedish study. The intake of tricyclic antidepressants over long periods of time and/or prior to birth may cause neonatal withdrawal symptoms (irritability, tachycardia, tachypnea, hypertonia, and convulsions).

N06AB – Selective inhibitors of serotonin – re-captation

Retrospective cohort studies with internal controls

- Simon et al (2002): 185 newborns exposed to SSRI (129 fluoxetine, 32 setraline, 28 paroxetine), and 185 controls. 12 exposed newborns had congenital major defects, vs. 9 among controls (RR = 1.4; CI 95%: 0.6-3.3); 18 exposed newborns had congenital minor defects, vs. 16 among controls (RR = 1.1; CI 95%: 0.6-2.3). Period of exposure is not specified.

Prospective cohort studies without controls

- Hendrick et al (2003): 138 exposures to SSRI throughout pregnancy (73 fluoxetine, 36 setraline, 19 paroxetine, 7 citalopram and 3 fluvoxamine). 2 newborns had congenital anomalies (Hirschsprung disease, cavum septi pellucidi) with an incidence of 1.4%. Low weight at birth had higher percentage: 2.9%.

Prospective cohort studies with internal controls

- Kullin et al (1998), 9 TIS USA and Canada: 267 first trimester exposures to SSRI (147 sertraline, 97 paroxetine, 26 fluvoxamine, 1 sertraline + fluoxetine, and 2 paroxetine + sertraline), 267 controls. 9 exposures showed congenital anomalies of different type and nature out of 222 newborns, vs. 9 out of 235 controls. RR = 1.0 (CI 95%: 0.5-2.6).

Prospective cohort studies with external controls

- Ericson et al (1999): 533 exposures to SSRI (15 fluoxetine, 365 citalopram, 119 paroxetine, and 34 sertraline). 21 newborns exposed to SSRI showing congenital anomalies vs. 18.7 expected (RR = 1.1; CI 95%: 0.7-1.7).

Case control studies, specific, nested in the cohort of all newborns

- Kallen and Ottenblad Olausson (2003), Swedish MBR: 5,015 newborns with cardiovascular defects exposed to SSRI, 23 controls. 577,730 total newborns, 2,820 exposed. OR of cardiopathy for first trimester exposure = 1.0 (CI 95%: 0.6-1.4).

Feto-neonatal effects: withdrawal symptoms (jaundice, irritability, hypertonia, and tremors) (Spencer 1993, Goldstein 1995, Kent et al 1995, Chambers et al 1996, Dahl et al 1997, Nijhuis et al 2001, Nordeng et al 2001, Costei et al 2002, Jaislaw et al 2003, Australian Adverse Drug Reactions Bulletin 2003); increase of miscarriages (Baum and Misri 1996); lower APGAR at birth and lower rates of psychomotor development vs. nonexposed (Casper et al 2003).

Fluoxetine – N06AB03

It has a half-life of 2-3 days, but in case of prolonged treatment it can reach 7 days; its active metabolite (norfluoxetine) has a half-life of 7-9 days. It is available in Italy since 1995.

Systematic review

- Addis and Koren (2000): research in Medline, Embase and other relevant sources updated to August 1996. Studies with or without controls dealing with malformations and first trimester exposure to fluoxetine prospectively recorded, prior to outcome were considered. 4 out of the 31 papers (including editorials, reviews, case reports and retrospective studies) concerning fluoxetine in pregnancy by Patuszak et al 1993, and Chamber et al 1996 (with controls), by Brunel et al 1994, and McElhatton et al 1996 (without controls), met the requirements to be included in the research. An overall of 7 defects (2 DIV, DIA, hypospadias, intestinal stenosis, nasal dermal sinus, and coccygeal dermal sinus) out of 367 exposures were detected, and the assessed malformation incidence was of 2.6% (CI 95%: 1.0-4.2). OR given by the two controlled studies was of 1.3 (CI 95%: 0.5-3.6).

Case report

- Vendittelli et al (1995): 1 first trimester exposed newborn with lipomeningocele. He also reports a non-published similar case.

Prospective cohort studies without controls (not included in systematic review)

- Wilton et al (1998): 26 healthy exposures, 1 newborn with spina bifida and hydrocephaly.

Retrospective cohort studies without controls

- Goldstein (1993), Goldstein et al (1997): spontaneous recordings (including a very small RCT) by manufacturer Eli Lilly of first trimester exposed pregnancies to fluoxetine, recorded prior to outcomes. Of 2,072 records, 768 were lost at follow-up. 24 out of 796 newborns had congenital anomalies (1 cardiovascular, 2 craniofacial, 4 gastrointestinal, 6 genitourinary, 3 defects of neural tube, 4 other defects, and 5 chromosomal syndromes) with an incidence of 3.5%, vs. 3.5-5% of the population. Some overlapping possibly occurred between this case report and the one included in the above-mentioned review.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 109 first trimester exposures to fluoxetine, 2 newborns with major defects, 5 expected: RR = 0.4 (CI 95%: 0.0-1.4).

Feto-neonatal effects: for exposure late in pregnancy, withdrawal symptoms (see general class); premature birth: ARR = 4.8 (CI 95%: 1.1-20.8) (Chambers et al 1996); difficult neonatal adaptation: ARR = 8.7 (CI 95%: 2.9-26.6); no differences in IQ vs. exposed to tricyclic agents and vs. nonexposed controls (Nulman et al 1977); lack of neurobehavioral anomalies at 4 and 6 years of age (Mattson et al 1999).

Citalopram – N06AB04

Its half-life is of about one day. It is available in Italy since 1994.

Case report

- Seifritz et al (1993): one fetus exposed in the early 6 weeks of gestation did not show gross birth defects
- Heikkinen et al (2002): 10 healthy newborns exposed throughout pregnancy.
- Laine et al (2003): 9 healthy newborns exposed in the first trimester.

Case control studies, specific, nested in the cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 newborns with cardiovascular defects, 10 of which exposed to citalopram; 577,730 newborns in overall, 1,419 of which exposed. OR for cardiopathy in first trimester exposure = 0.8 (CI 95%: 0.5-1.6).

Feto-neonatal effects: withdrawal symptoms were detected in exposures late in pregnancy (see general class). Psychological development was regular (Heikkinen et al 2002).

Paroxetine – N06AB05

Its half-life is of about one day. It is available in Italy since 1992.

Cohort studies without controls

- Inman et al (1993): of 63 first trimester exposures, 9 miscarriages, 12 abortions, and 9 healthy newborns.
- Rosa (1995): none of 52 exposures recorded by manufacturer had congenital anomalies.

Feto-neonatal effects: withdrawal symptoms were noticed, due to exposure late in pregnancy (see general class). Intraventricular hemorrhage (Canadian Adverse Drug Reaction 1997, Duijvestijn et al 2003), convulsions and subarachnoid hemorrhage (Salvia Roiges et al 2003), and premature birth (Unfred et al 2001) were also uncovered.

Sertraline – N06AB06

It is available in Italy since 1993.

Prospective cohort studies with internal controls

- Chambers et al (1999), California TIS: 112 exposures to sertraline, 191 controls. Incidence of major birth defects in exposures: 3.8% (4 newborns had congenital anomalies: bilateral choanal atresia, pulmonary stenosis, aneurysm of interatrial septum, clubfoot and VIP for Down syndrome) vs. 1.9% in controls.

Feto-neonatal effects: withdrawal syndrome for late in pregnancy exposure (see general class), and nystagmus (Oca et al 1999).

Fluvoxamine – N06AB08

Its half-life is of about one day. It is available in Italy since 1998.

Prospective cohort studies without controls

- Edwards et al (1994): 7 healthy newborns (one couple of twins) exposed in the first trimester
 - Wilton et al (1998): 11 healthy newborns exposed in the 1st trimester.

N06AB Conclusions: We have several studies in literature relevant to agents belonging to this therapeutic class, particularly fluoxetine, and their outcomes do not suggest an increase in congenital anomalies. The hypothesis of a low risk increase for DTN, not uncovered in some studies lacking controls, and not detected in available controlled studies – probably due to scarce statistic power, cannot be completely denied and deserves further studies. When their use covers long periods and/or they are administered just before birth withdrawal symptoms (jaundice, irritability, tremors and hypertonia) may be caused.

N06AX – More antidepressants

Oxitriptane (L-5-hydroxitriptofane) – N06AX01

This direct predecessor of serotonin crosses hematoencephalic barrier and is totally converted into serotonin. It is available in Italy since 1980.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: No studies have been found in literature relevant to the use of oxytryptane in pregnancy. The sole argument in case of exposure is the pharmacological analogy with serotonin and the lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

Mianserin – N06AX03

This is a tetracyclic compound. It is a selective antagonist of alpha-2 adrenergic receptors releasing noradrenaline; serotonin-antagonist in post-synaptic activity, it is not anticholinergic. Patented in 1977.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: We have been unable to find specific studies on the use of Mianserin. IN case of exposure the following topics should be considered: pharmacological analogy with antidepressants with similar activity, and lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

Trazodone – N06AX03

This phenylpiperazine inhibits re-captation of noradrenaline and serotonin blocking serotonergic receptors in synapse. Patented in 1966.

Case report

- Froberg et al (1994): 1 fetus exposed to trazodone in the first 16 weeks of pregnancy, with mediastinal teratoma and hydrops.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 112 first trimester exposures, 1 newborn had major defects, 4 expected. RR = 0.2 (CI 95%: 0.0-1.4).

Prospective cohort studies with internal controls

- Einarson et al (2003), TIS Motherisk Program: 58 first trimester exposures to trazodone and 89 to nefazodone (2 newborns with congenital anomalies); 147 exposures to antidepressants; 147 exposures to nonteratogenic drugs. 121 live births among exposures (82.4%), two of which with congenital anomalies (1.6%), 20 miscarriages (13.6%), 6 VIP (4%). No statistically significant difference among the 3 groups, as per incidence of congenital anomalies, miscarriage, VIP, pre-term birth, and neonatal weight.

Conclusions: We have very limited specific studies concerning the use of trazodone. In case of exposure the following topics should be considered: pharmacological analogy with antidepressants having a similar activity, and lack of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in database).

Mirtazapine – N06AX11

This is a tetracyclic antidepressant, antagonist of alpha-2 receptors in central pre-synapse increasing noradrenergic neurotransmission. It is available in Italy since 1996.

Case report

- Simhandl et al (1998): 1 healthy newborn exposed in the first trimester.
- Saks (2001): 7 healthy newborns for maternal hyperemesis in the first trimester.
- Kesim et al (2002): 2 healthy newborns exposed in the first trimester.

Cohort studies without controls

- Biswas et al (2003): 24 healthy newborns exposed in the first trimester.

Feto-neonatal effects: 3 healthy newborns exposed after the first trimester (Kesim et al 2002, Rohde et al 2003).

Conclusions: There are few records relevant to exposures to Mirtazapine and they all report healthy newborns. In case of exposure the following topics should be considered: pharmacological analogy with antidepressants having similar activity and lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

Venlafaxine – N06AX16

This bicyclic antidepressant is a strong inhibitor of serotonin re-captation and norepinephrine, but a weak inhibitor of dopamine re-captation. It is available in Italy since 1998.

Case report

- Ellingrod et al (1994): 4 healthy newborns exposed in early pregnancy.

Prospective cohort study without controls

- Okotore et al (1999): 46 exposures to venlafaxine in the first trimester: 1 newborn had a major birth defect not specified and 6 minor defects.

Prospective cohort studies with internal controls

- Einarson et al (2001), 7 TIS two of which in Italy: 150 exposures to venlafaxine, 150 controls exposed to nonteratogenic drugs. 18 miscarriages (12%), 7 VIP for reasons other than medical, 125 healthy newborns, 2 newborns with congenital anomalies (1.6%) (hypospadias; neural tube defect and clubfoot), in the group exposed to venlafaxine. 16 miscarriages (10.7%), 10 VIP for reasons other than medical, 121 healthy newborns, 3 newborns with congenital anomalies (2.4%) (defect of intraventricular septum; pyloric stenosis; absence of corpus callosum), in the group exposed to SSRI. In the controls exposed to nonteratogenic drugs: 11 miscarriages (7.3%), 2 VIP for non-medical reasons, 136 healthy newborns, and 1 newborn with congenital anomalies (0.7%) (cardiopathy). OR for congenital anomalies in offspring exposed to venlafaxine vs. exposed to SSRI = 0.7 (CI 95%: 0.1-4.0), vs. exposed to nonteratogenic drugs = 2.2 (CI 95%: 0.2-24.7).

Feto-neonatal effects: withdrawal symptoms for exposures in late pregnancy (de Moor et al 2003, Bloem et al 2003).

Conclusions: We have located information concerning about 200 newborns exposed to venlafaxine not suggesting risk increase of birth defects. In case of exposure we can advance the following further arguments: pharmacological analogy with antidepressants having similar activity, and lack of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in database).

Reboxetine – N06AX18

This is a highly selective and strong inhibitor of noradrenaline re-captation. It has a weak influence on serotonin re-captation, instead. It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Cozens et al (1988): nonteratogenic in rats and rabbits.

Conclusions: We have not located specific studies relevant to the use of reboxetine. In case of exposure the following should be considered: pharmacological analogy with antidepressants

having similar activity, and lack of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in database).

Ademethionine sulfate (S-Adenosylmethionine) – N06AX49

This molecule is naturally present in those organic tissues where it acts as donor of methyls. Exogenous ademethionine crosses hematoencephalic barrier, increases liquid concentration of ademethionine and turnover of serotonin and noradrenaline in brain. Patented in 1968.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Feto-neonatal effects: no neonatal adverse effects were noticed in 50 third trimester exposures (Ribalta et al 1991, Frezza et al 1990).

Conclusions: We have not located specific studies relevant to the use of ademethionine sulfate. In case of exposure the following should be considered: its nature and the lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

Hypericum perforatum – N06AX49

It is available in Italy since 2000.

Case report

- Grush et al (1988): 2 healthy newborns exposed at the beginning of pregnancy.

Studies on laboratory animals

- Christensen et al (1999): no adverse effects on the growth or physical development of mice at doses equivalent to human.
- Rayburn et al (2001): nonteratogenic in mice (180 mg/kg/day).

Conclusions: We have not located specific studies relevant to the use of hypericum. In case of exposure the following should be considered: analogy with similar antidepressants and lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

N06B – Psychostimulants and nootropic drugs

N06BA – Central-act sympathomimetic drugs

Modafinil – N06BA07

Its activity being not clear, yet, a possible interaction with gabaergic system has been considered. It is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: We have not located specific studies relevant to the use of this agent in human pregnancy; the sole possible evaluation is therefore based on laboratory animals' studies that have not uncovered teratogenic activity (records provided by manufacturer for registration, not available in database).

N06BX – More Psychostimulants and nootropic drugs

Piracetam – N06BX03

It increases ATP use. Patented in 1964.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Terekhina and Kruglova (1987): nonteratogenic in rats (100 mg/kg/day).

Feto-neonatal effects: no neonatal adverse effects were noticed in offspring exposed at the end of pregnancy to prevent respiratory distress (Hofmeyer and Kulier 2000 and 2002; Huaman et al 1983).

Citicoline – N06BX06

Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Aniracetam – N06BX11

Pyrrolidone derivative. It is available in Italy since 1991.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Acetylcarnitine (Levocarnitine Acetyl) – N06BX12

This isomer of a natural substance present in human body is structurally similar to acetylcholine. It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Idebenone – N06BX13

Benzoquinone derivative. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Ihara et al (1985): nonteratogenic in rats (500 mg/day).

Pramiracetam – N06BX16

It is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Olamine (alfoscerate) – N06BX49

It participates in the synthesis of membrane phospholipids and of acetylcholine. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Allgod et al (1991): nonteratogenic in rats up to 250 mg/kg/day.

N06BX Class Conclusions: We have been unable to locate specific studies relevant to the use of drugs in this class in human pregnancy. The sole useful arguments in case of exposure are therefore: the long period of commercialization – for some of them, the nature of some substances and, for all, the lack of teratogenicity in laboratory animals (records provided by manufacturer for registration, not available in database).

N06CA – Antidepressants in association with psychoactive drugs

Tranilcipromine – N06CA49 – N06AF04

This is an irreversible inhibitor of monoamine-oxidase enzyme. It is available in Italy since 1996.

Case report

- Bergamaschi et al (1968): one newborn with sacral-coccygeal teratoma exposed to tranilcipromine during pregnancy.
- Kennedy et al (2000): 2 newborns exposed to high dose of tranilcipromine had hypertelorism and cardiopathy. Placental infarct occurred in both cases and authors suggest that the defects may be due to a decrease of uteroplacental fluxus, caused by the drug. This outcome has been noticed also in sheep (Clark and Harrington 1982).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 21 exposures in the first 16 weeks to IMAO, 13 of which to tranilcipromine. 3 newborns had congenital anomalies. ARR for the entire considered class = 3.2 (CI 95%: 1.1-9.0).

Conclusions: He have been unable to find in literature specific studies relevant to the use of tranilcipromine, except for records of cases suffering from birth defects (that is not an evidence, but show the interest for teratogenic effects of drugs), and a very small cohort study. In case of exposure the sole valuable argument is the lack of teratogenicity in laboratory animals (records provided by manufacturer for registration, not available in database).

N07B – Drugs used in alienation disorders

N07BA – Drugs used in the control of nicotine addiction

Bupropion – N07BA02

It is available in Italy since 1996.

Prospective cohort studies without controls

- Glaxo Wellcome Bupropion Pregnancy Registry (2003), September 1997 – February 2003: 9 newborns with congenital anomalies (7 cardiopathy, 1 bilateral club foot, 1 Klinefelter syndrome) out of 270 first trimester exposures. The manufacturer also reported 11 exposed newborns showing different congenital anomalies with no specific pattern.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 3 healthy newborns exposed in the first trimester.

Conclusions: There are limited specific studies in literature, relevant to the use of Bupropion in pregnancy. In case of exposure an increase in congenital anomalies is not likely, in consideration of the lack of anomalies over the long period of commercialization and of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

N07BB – Drugs used in the control of alcohol abuse

Disulfiram – N07BB01

Patented in 1930.

Case report

- Nora et al (1977): 2 first trimester exposures. In a couple of twins one newborn had VACTERL syndrome (radial aplasia, vertebral fusion, thracheoesophageal fistula), another newborn had reduced lower limbs.
- Gardner and Clarkson (1981): 1 newborn exposed in early pregnancy, monitored at the age of 10, had facial anomalies and mental retardation, that is anomalies possibly suggesting feto-alcoholic syndrome.
- Dehaene et al (1984): 1 newborn exposed in the first trimester with syndrome of Pierre Robin and cardiopathy (coronary defect).
- Helmbrecht and Hoskins (1993): 2 healthy newborns exposed in the first trimester.
- Reitnauer et al (1997): 2 monozygotic twins exposed in the first trimester, one with cleft palate, and the other with limbs defects.

Prospective cohort studies without controls

- Faure-Tissot and Delatour (1965): 2 healthy newborns, one miscarriage and 2 newborns with clubfoot.
- Jones et al (1991): of 13 first trimester exposures, the 7 newborns to mothers not taking alcohol were healthy, whereas 3 of the 6 newborns to mothers abusing alcohol had FAS, and the other 3 infants were healthy.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 25 first trimester exposures, 1 newborn had congenital defect, 1 expected. RR = 1.0 (CI 95%: 0.0-5.6).

Conclusions: We have not been able to find a sufficient number of studies to draw reasonable conclusions on the use of Disulfiram. In case of exposure the following arguments can be considered against a possible teratogenicity: clinical records regarding completely different among themselves defects, lack of teratogenicity in laboratory animals, and lack of anomalies over the long period of commercialization.

Naltrexone – N07BB04

This is a competitive opioid antagonist. Patented in 1966.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Nuite et al (1975), Christian (1984): nonteratogenic in rats and rabbits.

Conclusions: There are no specific studies in literature relevant to the use of this drug in human pregnancy, the sole possible evaluation being therefore based on laboratory animals' studies, which have not revealed teratogenic activity (records provided by manufacturer for registration, not available in database).

Metadoxine – N07BB49

It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are no specific studies in literature relevant to the use of this drug in human pregnancy, the sole possible evaluation being therefore based on laboratory animals' studies, which have not revealed teratogenic activity (records provided by manufacturer for registration, not available in database).

N07BC – Drugs used to control opioid abuse

Methadone – N07BC02

This is a narcotic analgesic.

Case report

- Erhart and Sinatra (1994): 1 newborn exposed in pregnancy to methadone had biliary atresia, intestinal malrotation, and craniofacial anomalies.

Cohort studies without controls

- Chavez et al (1979): of 146 newborns exposed to methadone, 20 (14%) had functional eye-disease (nystagmus, ocular torticollis, and strabismus).
- Brown et al (1997): of 32 exposures to methadone throughout pregnancy, 3 newborns had not specified congenital anomalies.

Feto-neonatal effects: The use of methadone late in pregnancy may cause neonatal withdrawal symptoms in 60-90% of the cases (shrill weeping, vomiting, diarrhea, fever, dishydration, convulsions) (Kandal and Gartner 1973, Zelson et al 1973, Blinick et al 1973, Newman et al 1973, Harper et al 1974, Strass et al 1974, Ostrea et al 1976, Harper et al 1977, Wilson et al 1981, Doberczak et al 1991, Mayes and Carroll 1993, Brown et al 1997, and Sinha et al 1999). Withdrawal symptoms usually start 48 hours following birth, but a small percentage of the offspring may develop it after 7-14 days (Zelson et al 1973, Challis and Scopes 1977). Here are more adverse effects recorded in offspring exposed to methadone: intrauterine growth retardation (Zelson et al 1973, Blinick et al 1973, Newman et al 1973, Kaltenbach and Finnegan 1989), increase in stillbirth and neonatal death (Rementeria et al 1973), sudden infant death syndrome (Pierson et al 1972, Chavez et al 1979), jaundice, thrombocytosis (Rementeria et al 1973, Burstein et al 1982), neurobehavioral disorders (Rosen e Johnson 1982), hyperphagia (Martinez et al 1999).

Conclusions: There are not many studies relevant to the use of methadone, but its outcomes are probably more experienced than what we can find in literature. Despite of the numerous adverse effects in offspring, they do not appear in the development of embryo.

N07CA – Preparations used in the treatment of vertigo

Betahistine – N07CA01

Its activity is similar to histamine. Patented in 1966.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Cinnarizine – N07CA02

This is a piperazine derivative, H1 antagonist with anticholinergic central activity, and calcium channel blocking activity. It is available in Italy since 1970.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kovatsis et al (1972): cinnirazine did not increase congenital anomalies in guinea pigs.

Flunarizine – N07CA03

It is a peripheral vasodilator, antihistaminic, and it has a calcium entry blocking activity. It is available in Italy since 1981.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

Miyazaki et al (1982): Flunarizine did not increase congenital anomalies in rats and rabbits treated with 30 and 36 mg/kg/day per os, respectively.

N07CA Class Conclusions: There are no specific studies in literature relevant to the use in human pregnancy of agents belonging to this therapeutic class. The sole possible evaluation is therefore based on laboratory animals, which have not uncovered any teratogenic action (records provided by manufacturer for registration, not available in database).

N07XX – More drugs used for nervous system

Diencephalon phosphates – N07XX49

It is available in Italy since 1996.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Politreline – N07XX49

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

N07XX49 Class Conclusions: There are no specific studies in literature relevant to the use in human pregnancy of agents belonging to this therapeutic class. The sole possible evaluation is therefore based on laboratory animals, which have not uncovered any teratogenic action (records provided by manufacturer for registration, not available in database).